Sex Differences in Diabetes impact on ASCVD and HF

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Disclosures

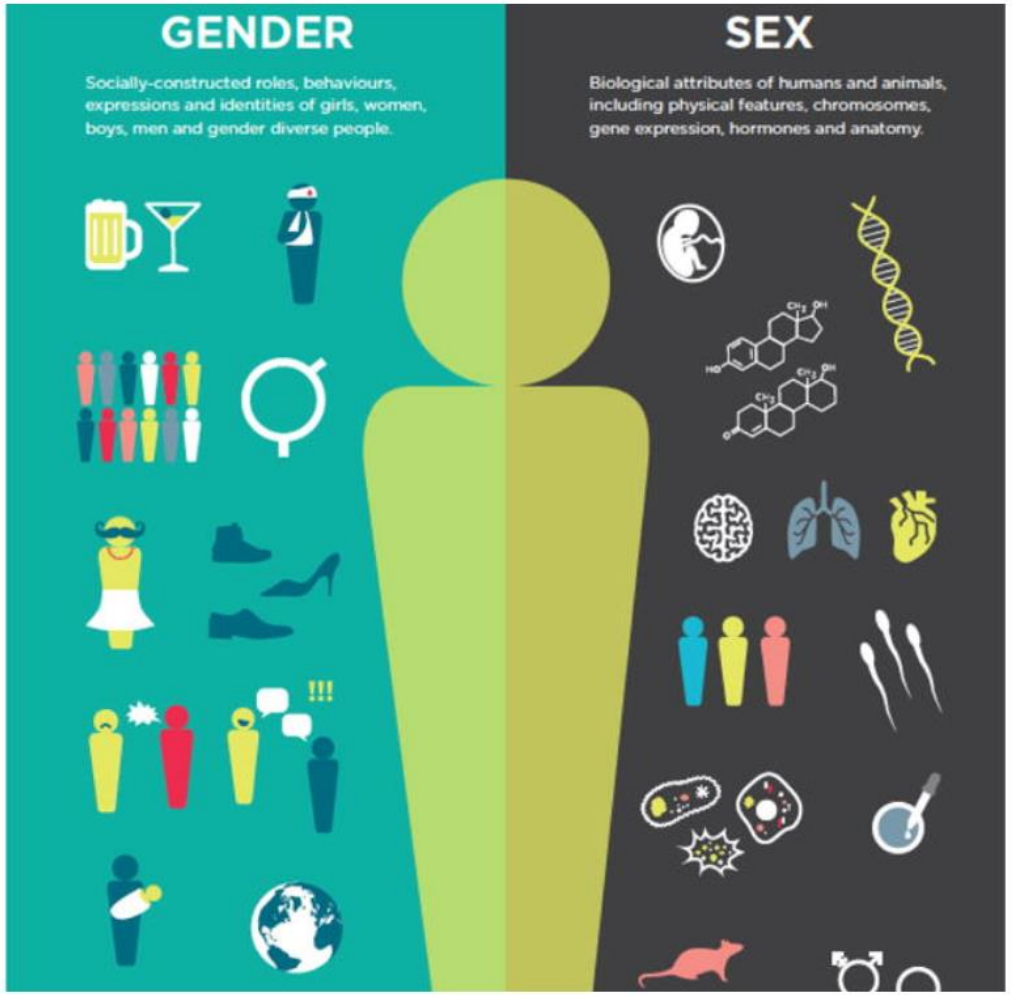
- Dr. Michos reports serving on Advisory Boards for
  - AstraZeneca, Amarin, Bayer, Boehringer Ingelheim, Esperion, Novartis, Novo Nordisk, Pfizer

Sex vs. Gender

GENDER

Social/cultural

- Enacted roles and behaviors
- Identity



Sex

Biological

- Sex chromosomes
- Sex hormones
- Gene expression
- Anatomy

Humphries KH
Front Neuroendocrinol 2019

- **Health is determined by both biology and the expression of gender.**
- **Both Sex and Gender contribute to observed differences in women's CV health**

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Diabetes in Women: Epidemiology and contributions to CVD risk

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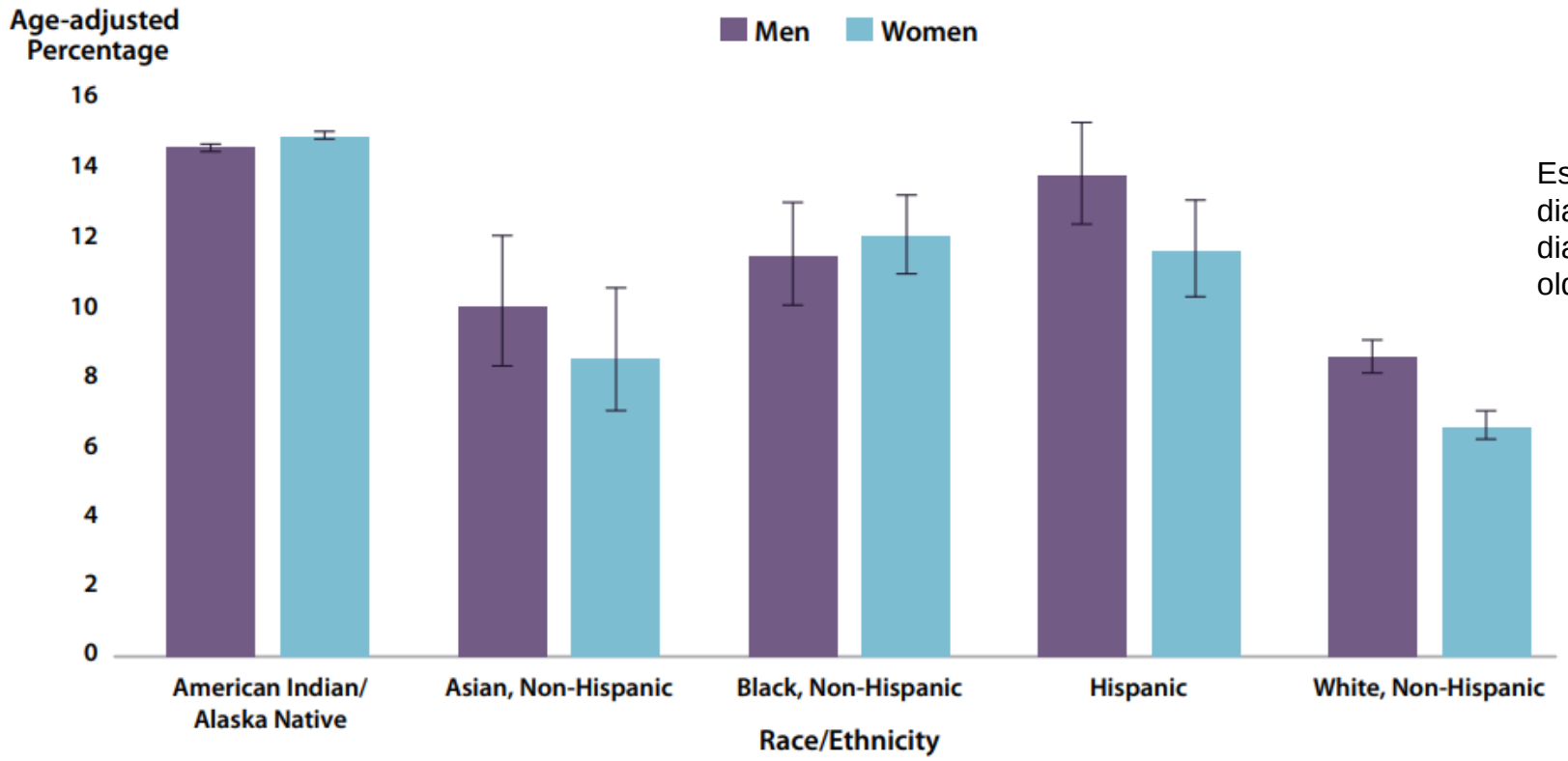
Men have higher prevalence of diabetes

Characteristic	Diagnosed diabetes Percentage (95% CI)	Undiagnosed diabetes Percentage (95% CI)	Total diabetes Percentage (95% CI)
Sex			
Men	11.0 (9.7–12.4)	3.1 (2.3–4.2)	14.0 (12.3–15.5)
Women	9.5 (8.5–10.6)	2.5 (2.0–3.2)	12.0 (11.0–13.2)



Estimated crude prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 2013–2016

CDC
https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

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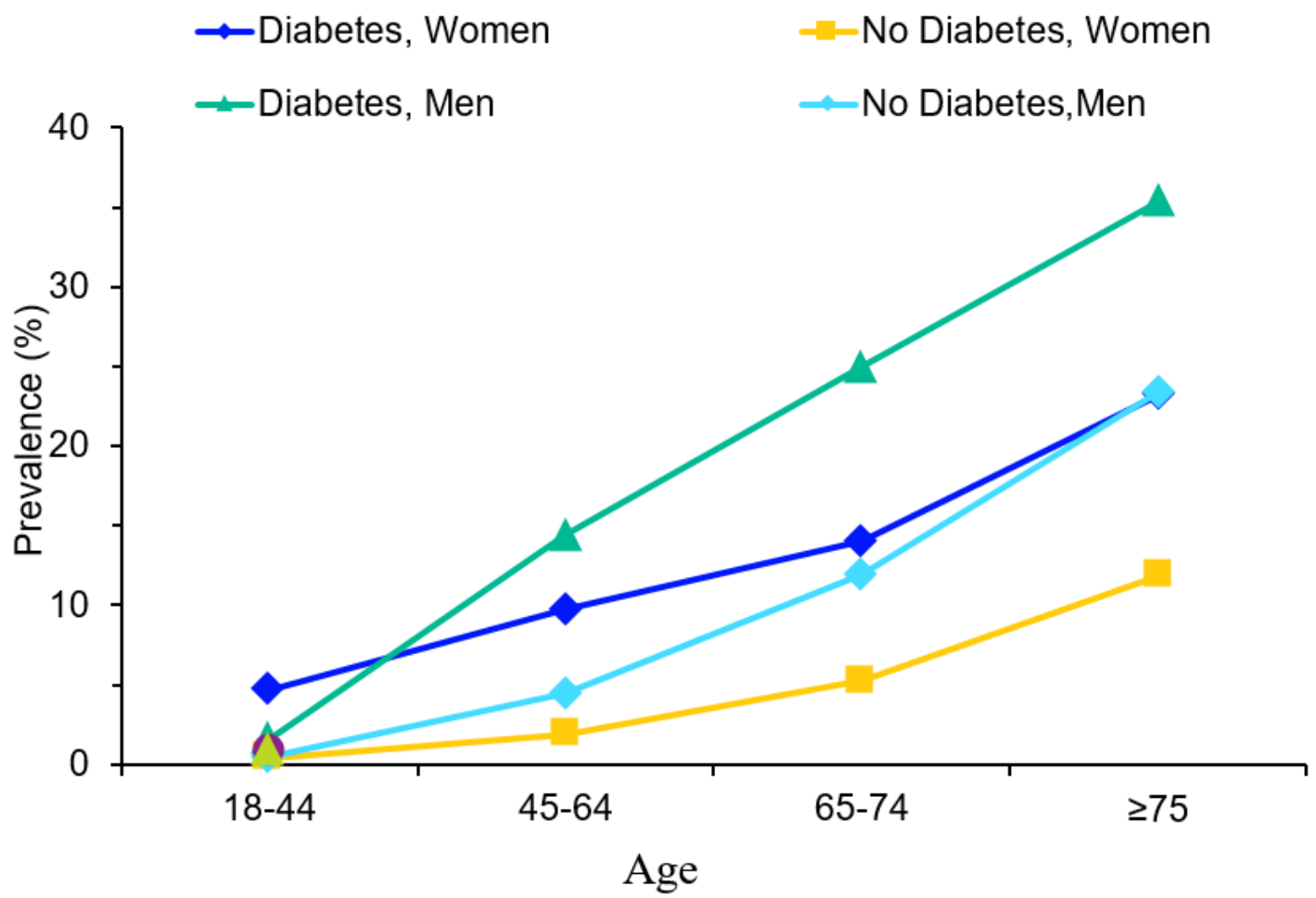
Prevalence of Coronary Heart Disease by Diabetes Status, Sex and Age, U.S. 2019-2020

CHD



Age-standardized* Prevalence of History of Heart Disease among Adults (≥18 years), by Diabetes Status and Sex, NHIS, U.S., 2019-2020

Coronary Heart Disease†

	Diabetes†	No Diabetes
Total	16.5 (0.60)	6.9 (0.20)
Sex		
Men	20.0 (0.94)	9.6 (0.36)
Women	12.9 (0.71)	4.7 (0.23)

Any Heart Condition, including Angina

	Diabetes†	No Diabetes
Total	20.6 (0.65)	9.3 (0.23)
Sex		
Men	24.8 (1.04)	12.3 (0.39)
Women	16.5 (0.78)	6.8 (0.27)

History of heart disease and diabetes status is self-reported.
* Standardized to the 2019-2020 NHIS diabetic population; categories include 20-44, 45-64, ≥65
† Self-reported

Source: 2019-2020 National Health Interview Survey

From "Diabetes in America", Chapter 18 Heart Disease. Kalyani RR…**Michos ED.** 2022 in press

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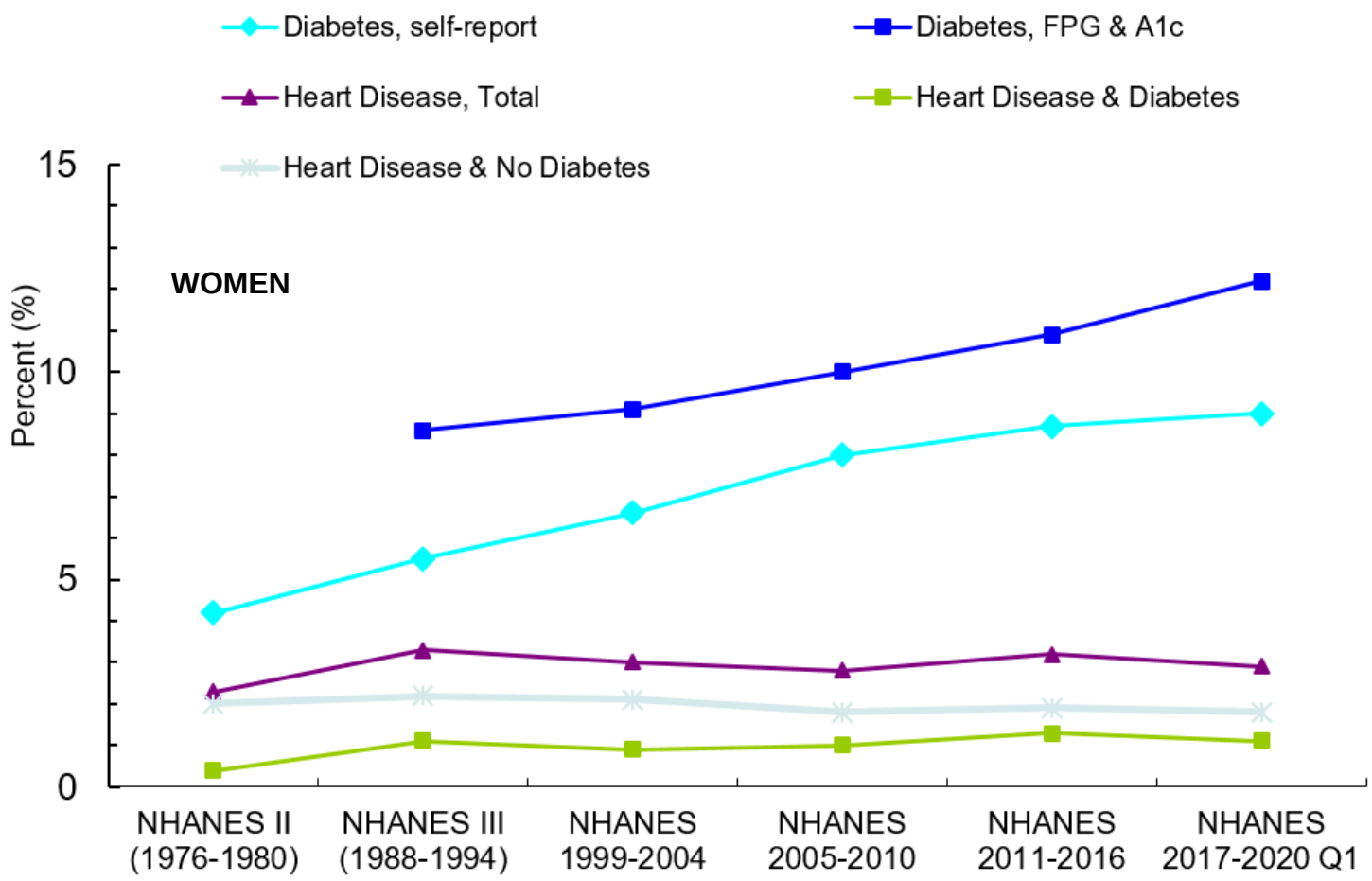
Trends in the prevalence of diabetes and heart disease among adult women, U.S., 1976-2020



From “Diabetes in America”, Chapter 18

Kalyani RR…**Michos ED.** 2022 in press

*Diabetes is defined as self-report or self-report and/or A1c (≥6.5%) and/or FPG (≥126 mg/dL); diabetes is self-reported when combined with heart disease
† Heart disease is self-reported and includes heart attack or heart failure
‡ Estimates are age-standardized to the 2019 NHIS total population
Source: National Health and Nutrition Examination Surveys

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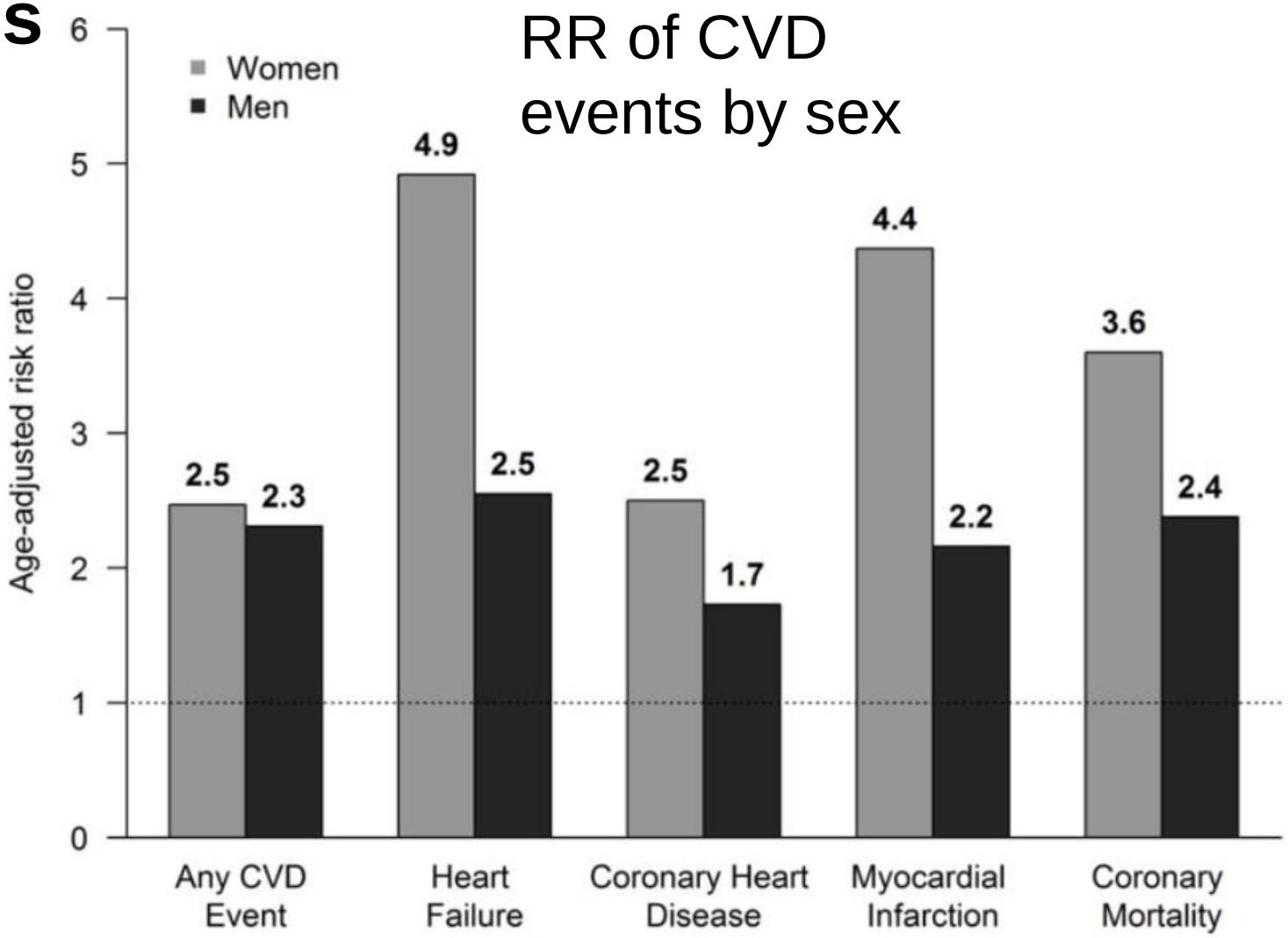
Diabetes Confers Greater Relative Risk of CVD in Women compared to Diabetes in Men

Diabetes

RR of CVD events by sex



Humphries KH
Front Neuroendocrinol 2019

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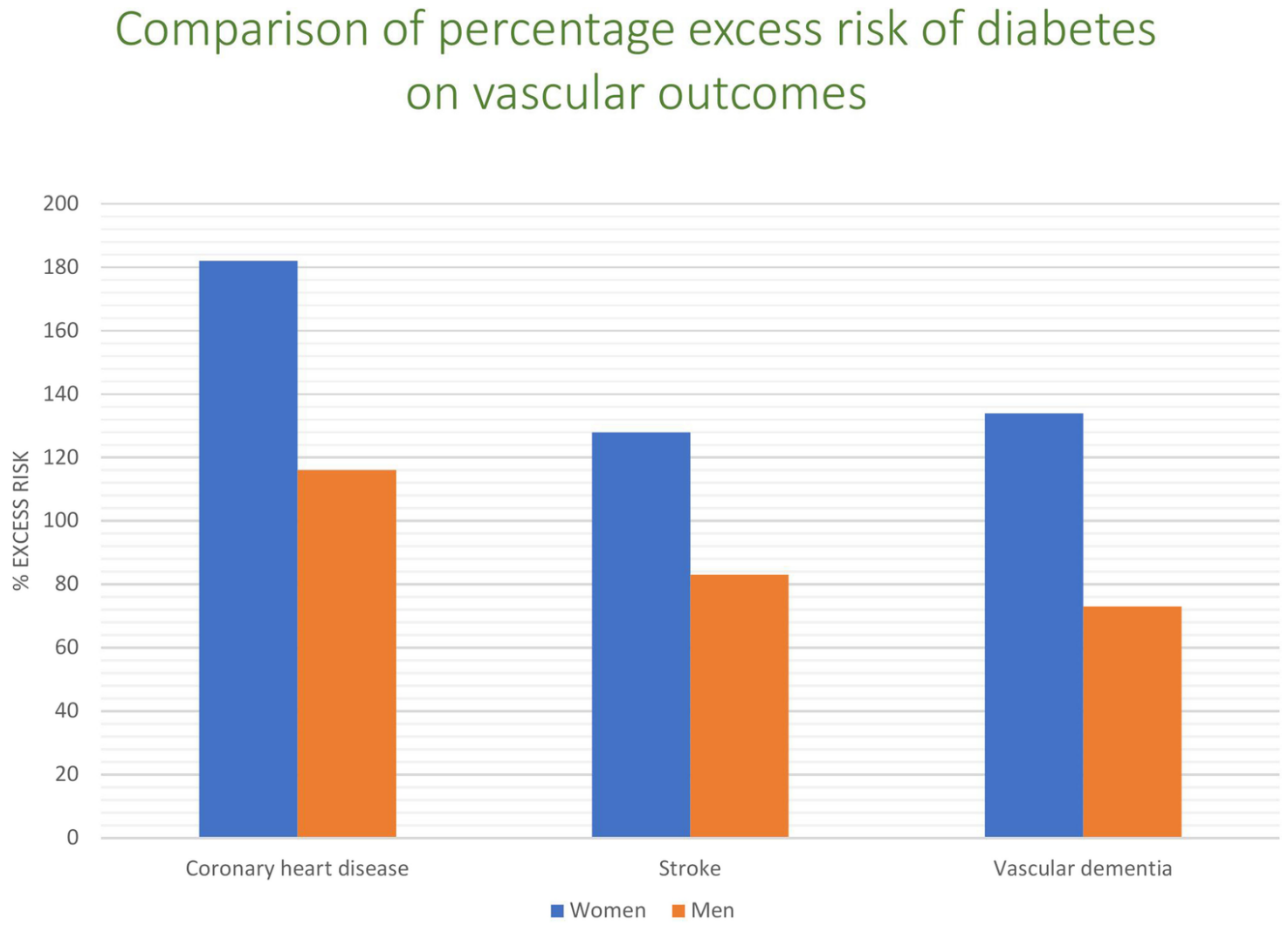
Excess vascular risk in women conferred by diabetes



Broni EK…**Michos ED**. Curr Diab Rep 2022;22(1):11-25

Comparison of percentage excess risk of diabetes on vascular outcomes between women and men with diabetes. Modified Open Access data from prior meta-analysis by de Ritter R, de Jong M, Vos RC, van der Kallen CJH, Sep SJS, Woodward M et al. 2020

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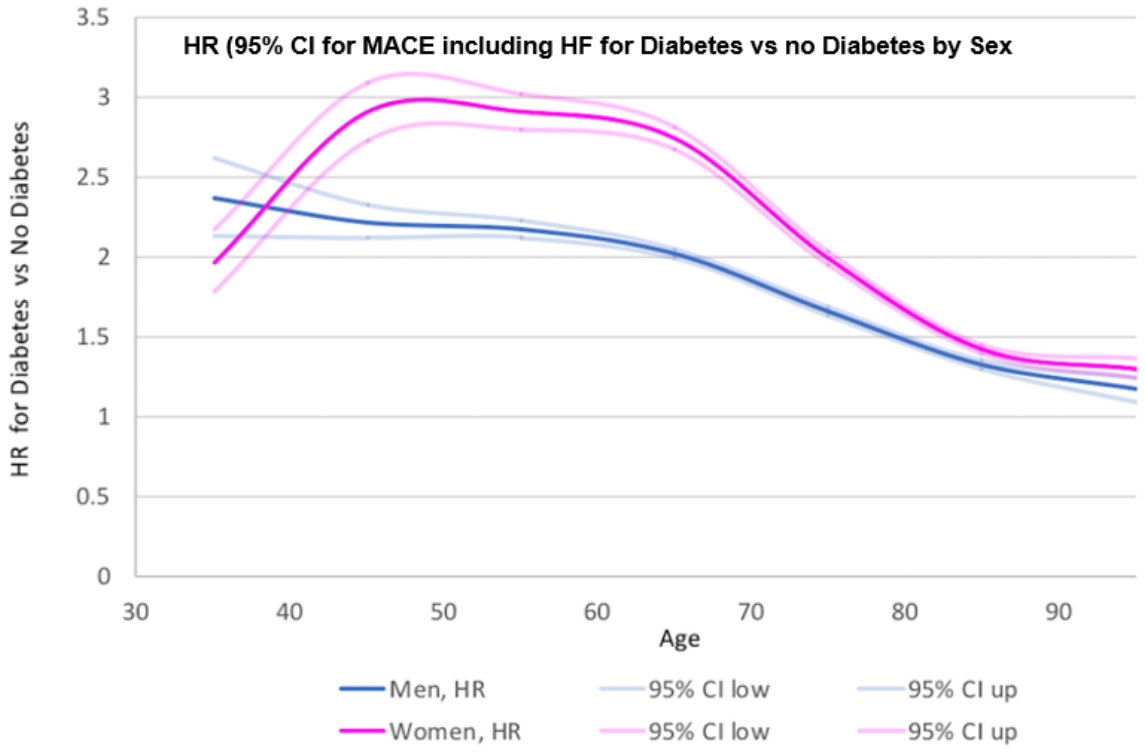
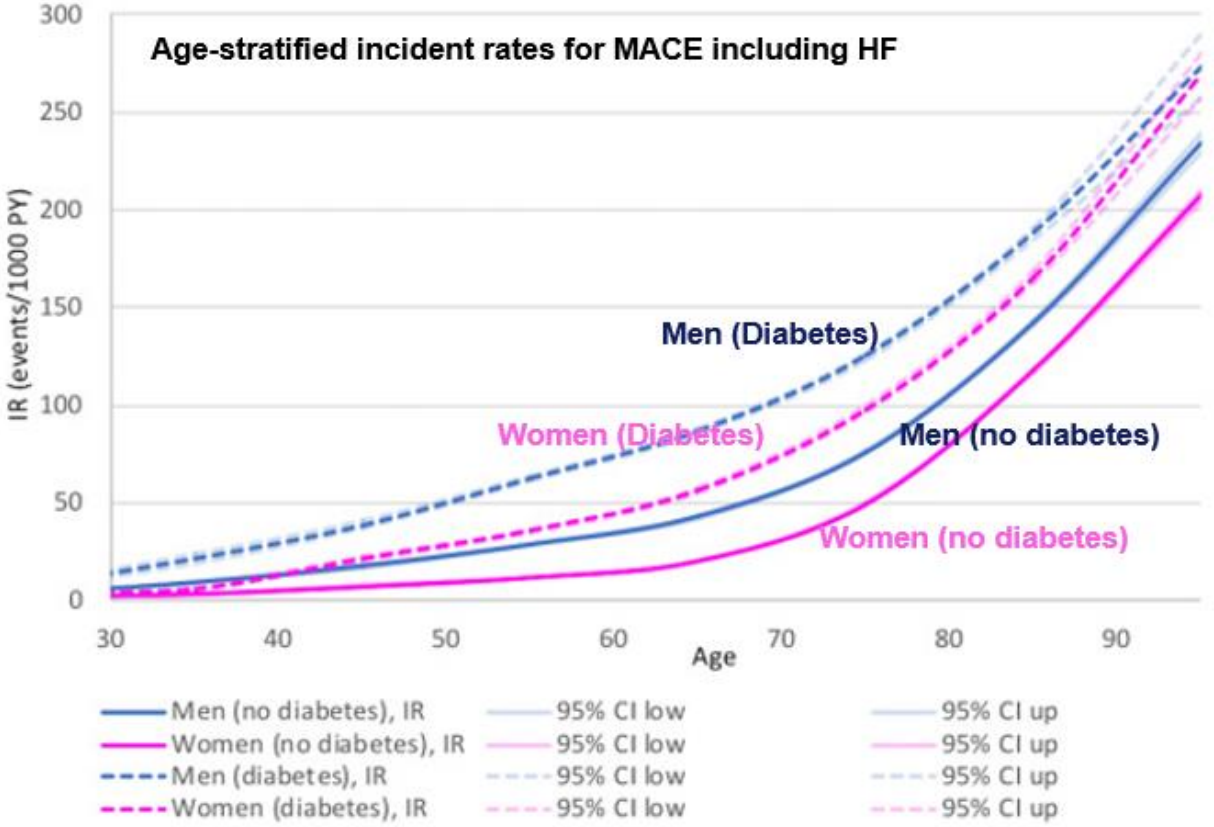
Relative vs Absolute Risk of CVD Attributable to Diabetes by Sex

- 2,953,816 individuals in France
- 349,928 (11.9%) had diabetes
- Follow-up at least 5 years
- Incident CVD: CV death, MI, stroke, HF

Relative hazard of CVD conferred by diabetes greater in women



Absolute Risk of CVD conferred by diabetes greater in men



Angoulvant et al. Diab Metab 2021; 47(5): 101226

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Diabetes-years and incident HF (ARIC) by sex

TABLE 3 Association for Diabetes Duration and Incident Heart Failure by Subgroups (Sex and Race) of ARIC Participants (Visit 4 1996-1998)

			Diabetes Duration, y				
	No Diabetes	Prediabetes	0 to <5	5 to <10	10 to <15	≥15	*P* Trend[a]
Sex							
Men							
Events	348	266	113	91	22	22	
IR (95% CI)	9.67 (8.71-10.75)	13.37 (11.85-15.08)	18.52 (15.40-22.27)	24.44 (19.90-30.01)	35.61 (23.45-54.09)	25.03 (16.48-38.01)	
HR (95% CI)	Ref.	1.13 (0.96-1.33)	1.46 (1.17-1.81)	2.07 (1.64-2.62)	2.75 (1.78-4.24)	1.39 (0.90-2.15)	<0.001
Sub-HR (95% CI)	Ref.	1.07 (0.91-1.27)	1.31 (1.05-1.64)	1.68 (1.31-2.15)	2.24 (1.45-3.45)	1.25 (0.79-1.99)	0.006
Women							
Events	413	368	107	129	29	60	
IR (95% CI)	8.04(7.30-8.85)	11.29 (10.20-12.51)	12.60 (10.42-15.22)	23.97 (20.17-28.48)	28.13 (19.55-40.48)	51.09 (39.67-65.80)	
HR (95% CI)	Ref.	1.18 (1.02-1.36)	1.14 (0.92-1.42)	1.90 (1.54-2.34)	1.78 (1.21-2.61)	4.49 (3.40-5.93)	
Sub-HR (95% CI)	Ref.	1.16 (1.01-1.34)	1.06 (0.84-1.33)	1.61 (1.29-2.00)	1.53 (0.98-2.38)	3.23 (2.31-4.52)	

- Among people with T2D, the duration of diabetes was significantly associated with an increased risk of incident HF.
- This association was stronger in women compared to men.

Echouffo-Tcheugui JB….**Michos ED**….Ndumele CE. JACC Heart Fail. 2021;9(8):594-603

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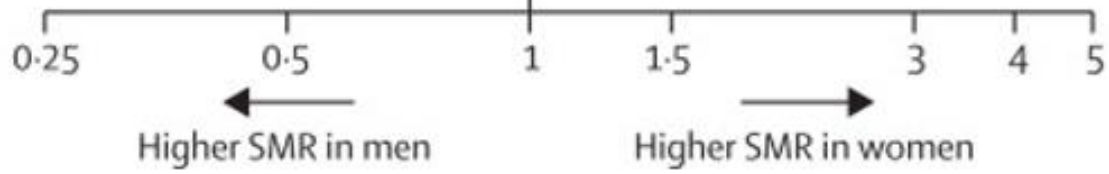
RR for CVD greater in women (compared to men) for Type 1 DM also

	Studies	Individuals	Events	Ratio of SMR (95% CI)
Coronary heart disease[10,12,27,31,39,40,44]	7	59 383	1427	2·54 (1·80–3·60)
Stroke[12,16,26,39]	4	45 677	371	1·37 (1·03–1·81)
Cardiovascular disease[10,12,17,21,28,33,39,40,42]	9	75 983	2166	1·86 (1·62–2·15)
Renal disease[10,21,28]	3	30 332	142	1·44 (1·02–2·05)
Cancer[21,28,33,39]	4	31 018	119	1·23 (0·79–1·98)
Accident and suicide[10,21,28,33,44]	6	36 320	260	1·34 (0·97–1·84)



Huxley RR et al, Lancet Diabetes & Endocrinology. 2015; 3(3): 198-206,

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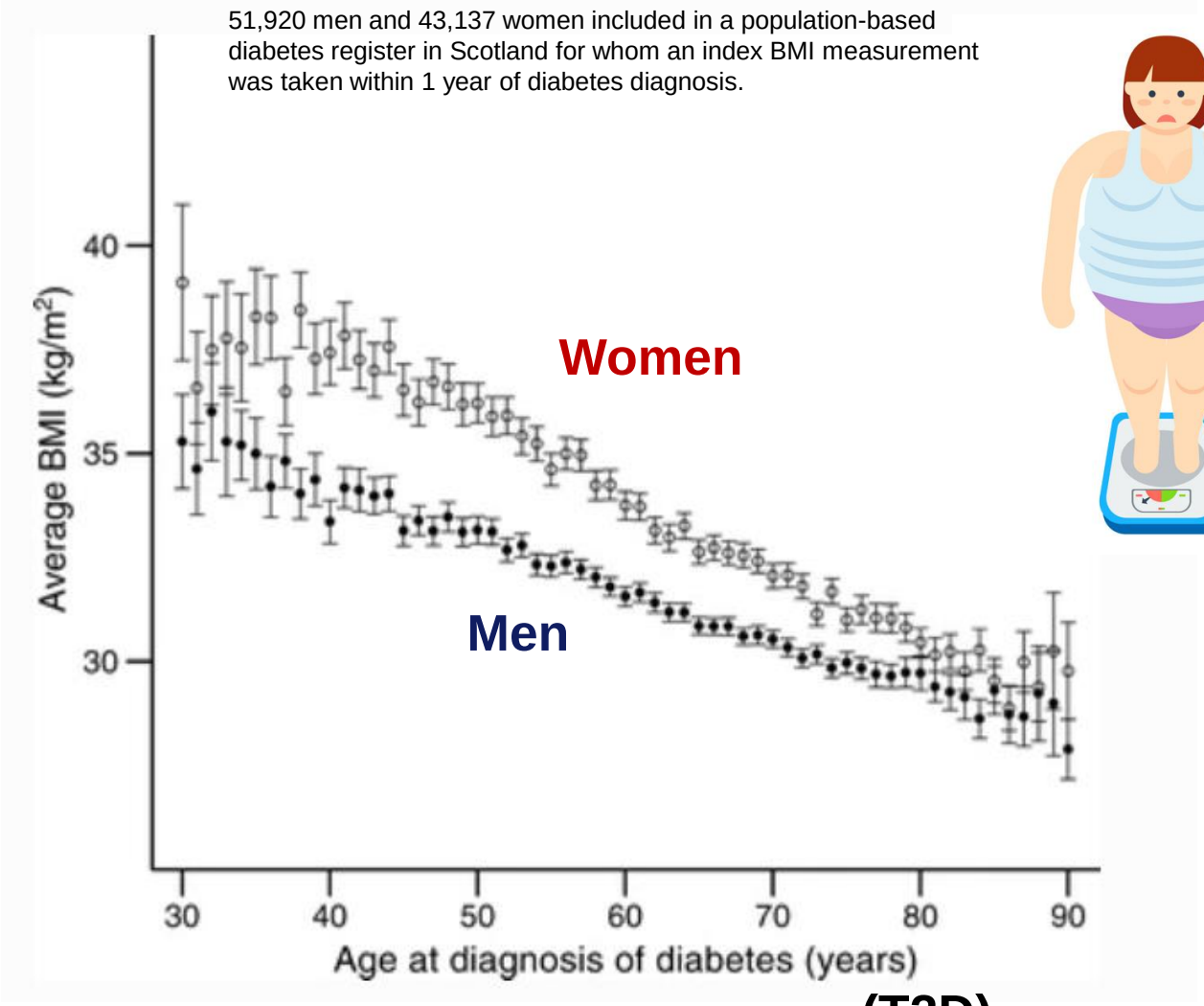
BMI is higher in women at diabetes diagnosis

51,920 men and 43,137 women included in a population-based diabetes register in Scotland for whom an index BMI measurement was taken within 1 year of diabetes diagnosis.



(T2D)

- Women with type 2 diabetes had to put on more weight to develop diabetes.
- This excess weight is associated with a greater deterioration in CV risk factor levels, endothelial dysfunction, low-grade inflammation, and hypercoagulability state in women as compared with men.

Al-Salameh A. Mayo Clin Proc.2019;94(2):287-308

Logue et al. Diabetologia 2011;54:3003-6.

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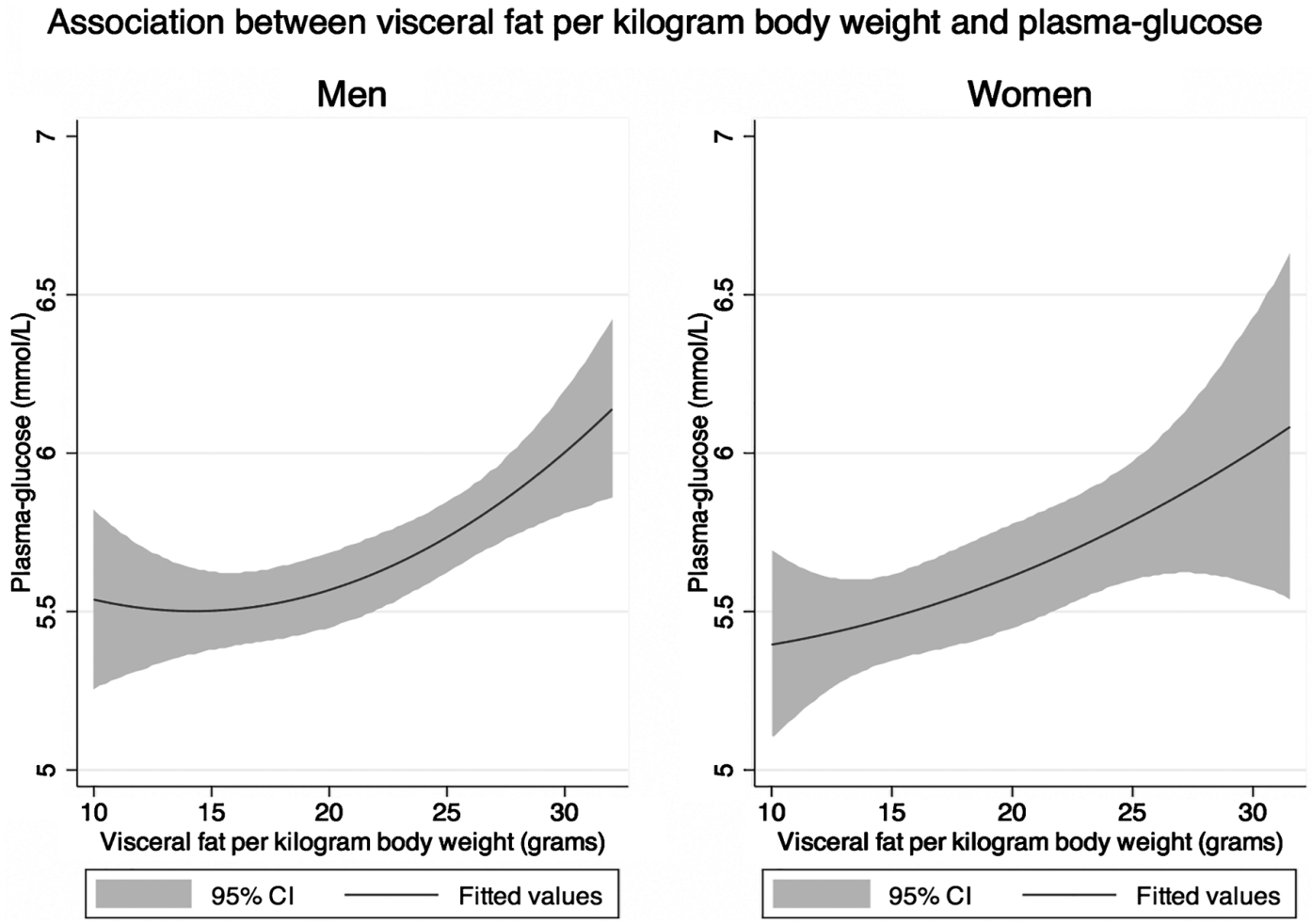
Visceral fat and diabetes risk by sex



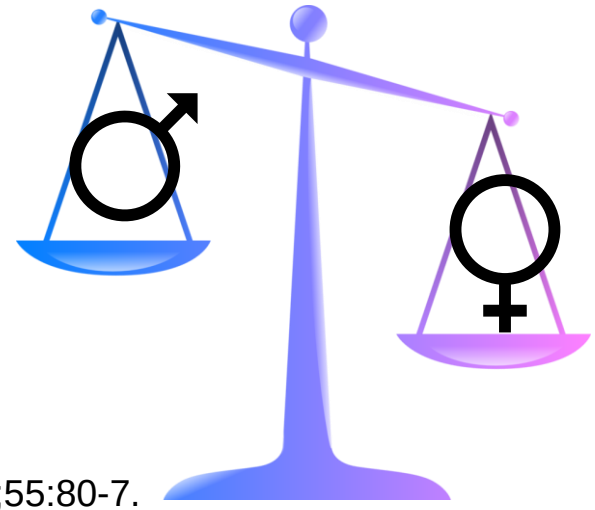
- This is largely driven by the fact that men have more visceral fat than women
- Men had approximately twice the odds of having type 2 diabetes compared with women (OR 1.95; 95% CI 1.38–2.76).
- However when visceral fat was included as a covariate, male sex was not associated with increased risk of type 2 diabetes (OR, 0.77; 95% CI, 0.51–1.18).

Norstrom A et al. J Clin Endocrinol Metab. 2016; 101 (10); 3740–3746,

Women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men

- Study of 7,529 individuals aged 60-79 free of CVD and compared prevalence of RFs by diabetes status and sex

- Sex-diabetes interaction significant ($p<0.05$) for:
  - BMI
  - Waist Circumference
  - Diastolic Blood Pressure
  - HOMA IR
  - Fasting Glucose
  - WBC
  - tPA
  - Factor VIII



Wannamethee et al. Diabetologia 2012;55:80-7.

- Greater adverse influence of diabetes on adiposity and HOMA-IR and downstream blood pressure, lipids, endothelial dysfunction and systemic inflammation in women compared with men
- May contribute to women's greater relative risk of coronary heart disease.

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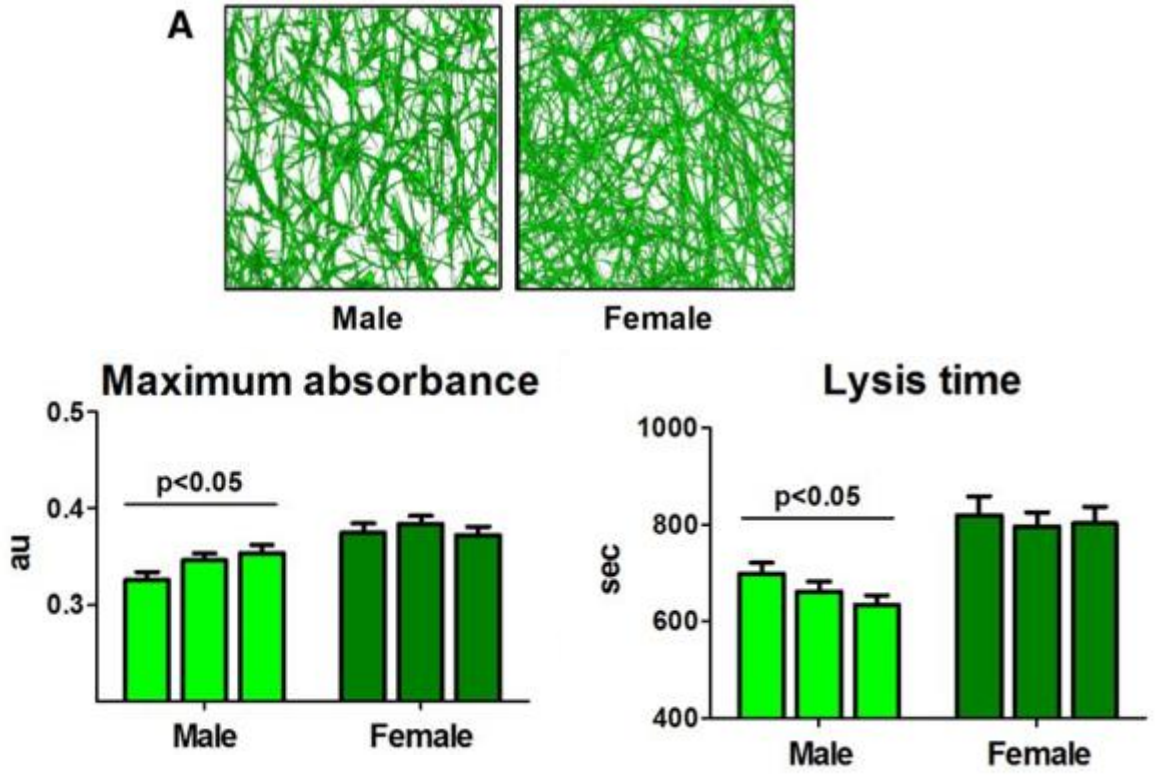
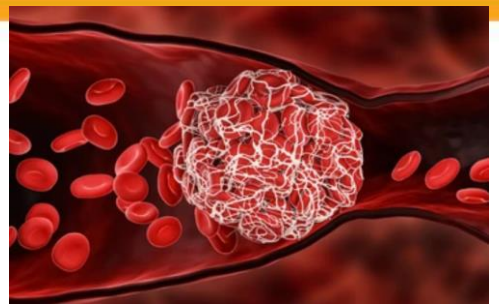
Prothrombotic phenotype in women with diabetes

Women with type 2 diabetes have compact clots with compromised fibrinolysis compared with men.



Alzahrani et al. J Clin Endocrinol Metab 2012;97: E2282-2287



- Women with T2D had higher levels of factor VII:C and plasminogen activator inhibitor-1 activity than men, and these differences remained significant after accounting for the higher BMI and A1c in women
- This may contribute to the increased CV risk of diabetes that is particularly marked in women.

Mansfield et al. Arterioscler Thromb Vasc Biol 1996;16:160-4

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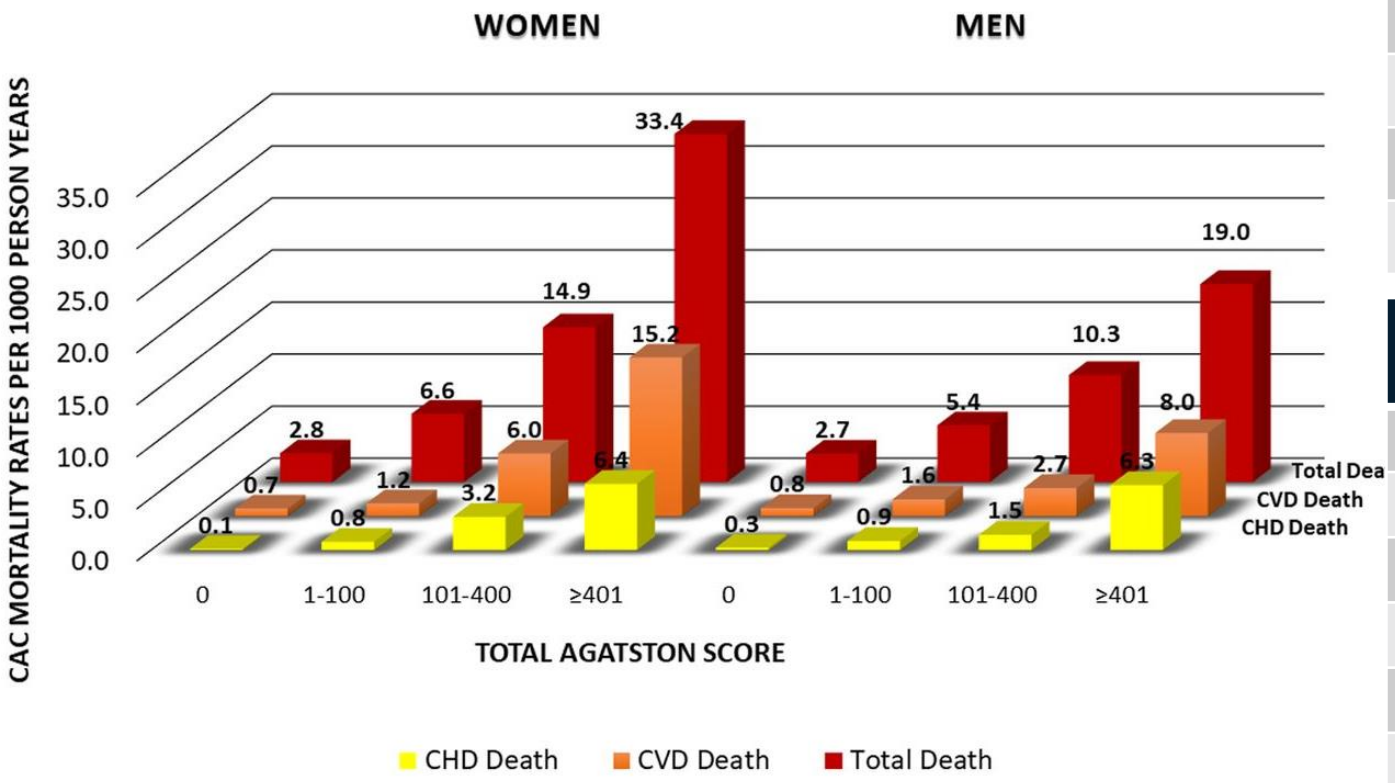
Among patients with diabetes, greater CAC predicts total and CVD mortality more strongly in women

- CAC Consortium cohort
- 4,503 adults with diabetes (32.5% women) aged 21–93 years
- CAC >0 in 61.2% of women & 80.4% of men (interaction *P*=0.01).



	Total Mortality (Adjusted HR and 95% CI)	
	MEN	WOMEN
CAC=0	Ref	Ref
CAC 1-100	1.36 (0.83-2.24)	1.43 (0.81-2.56)
CAC 101-400	1.88 (1.15-3.09)	2.56 (1.45-4.53)
CAC >400	2.61 (1.61-4.24)	4.05 (2.33-7.04)
P-interaction by sex 0.01		

	CVD Mortality (Adjusted HR and 95% CI)	
	MEN	WOMEN
CAC=0	Ref	Ref
CAC 1-100	1.36 (0.54-3.45)	0.96 (0.29-3.21)
CAC 101-400	1.63 (0.64-4.14)	3.67 (1.30-10.38)
CAC >400	3.48 (1.44-8.37)	6.27 (2.27-17.28)
P-interaction by sex 0.04		

Wong ND et al. Diabetes Care 2020;43:2597-2606

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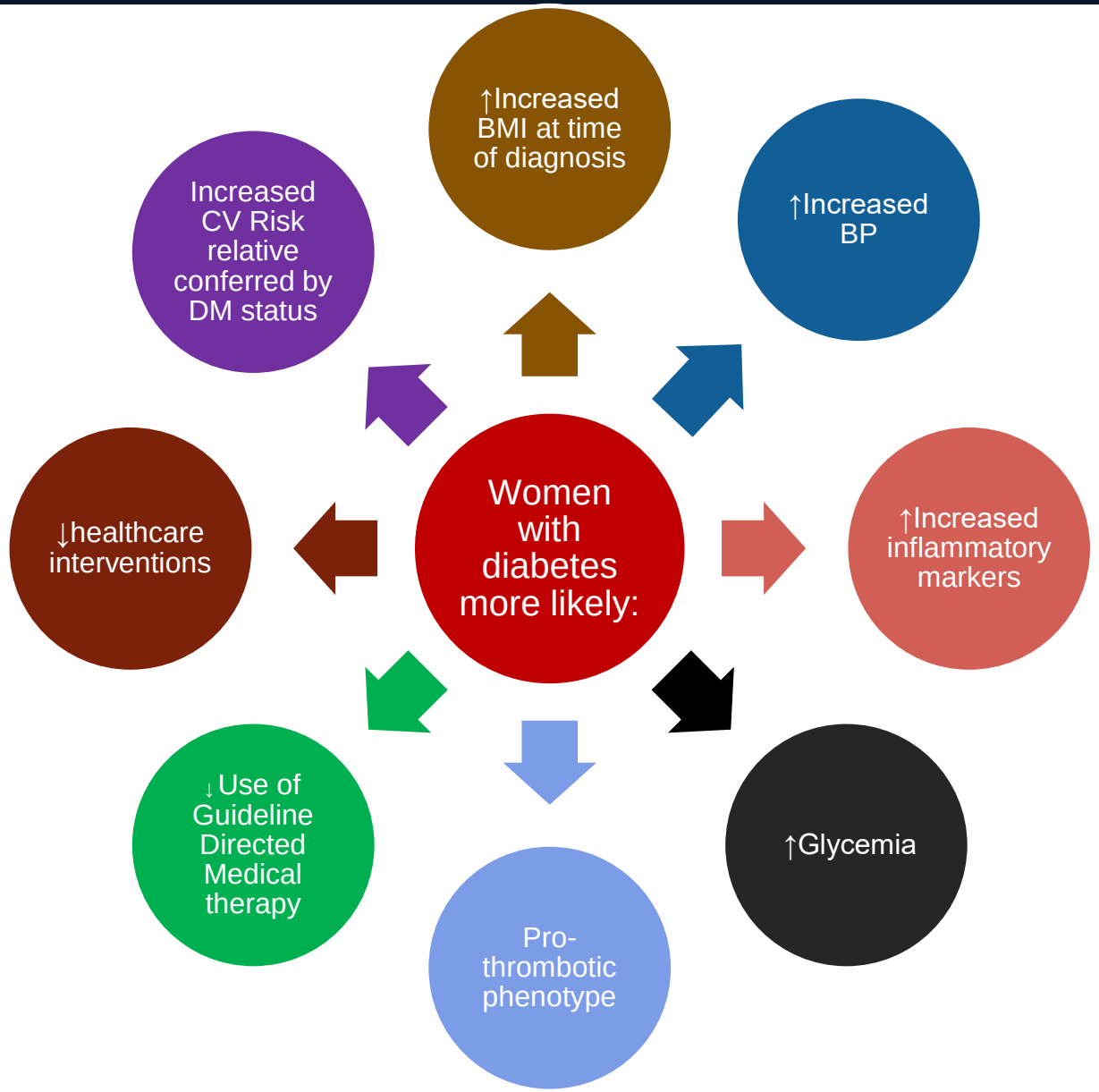
Mechanisms conferring greater CVD risk among women with diabetes



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Diabetes Therapeutics
Efficacy by Sex

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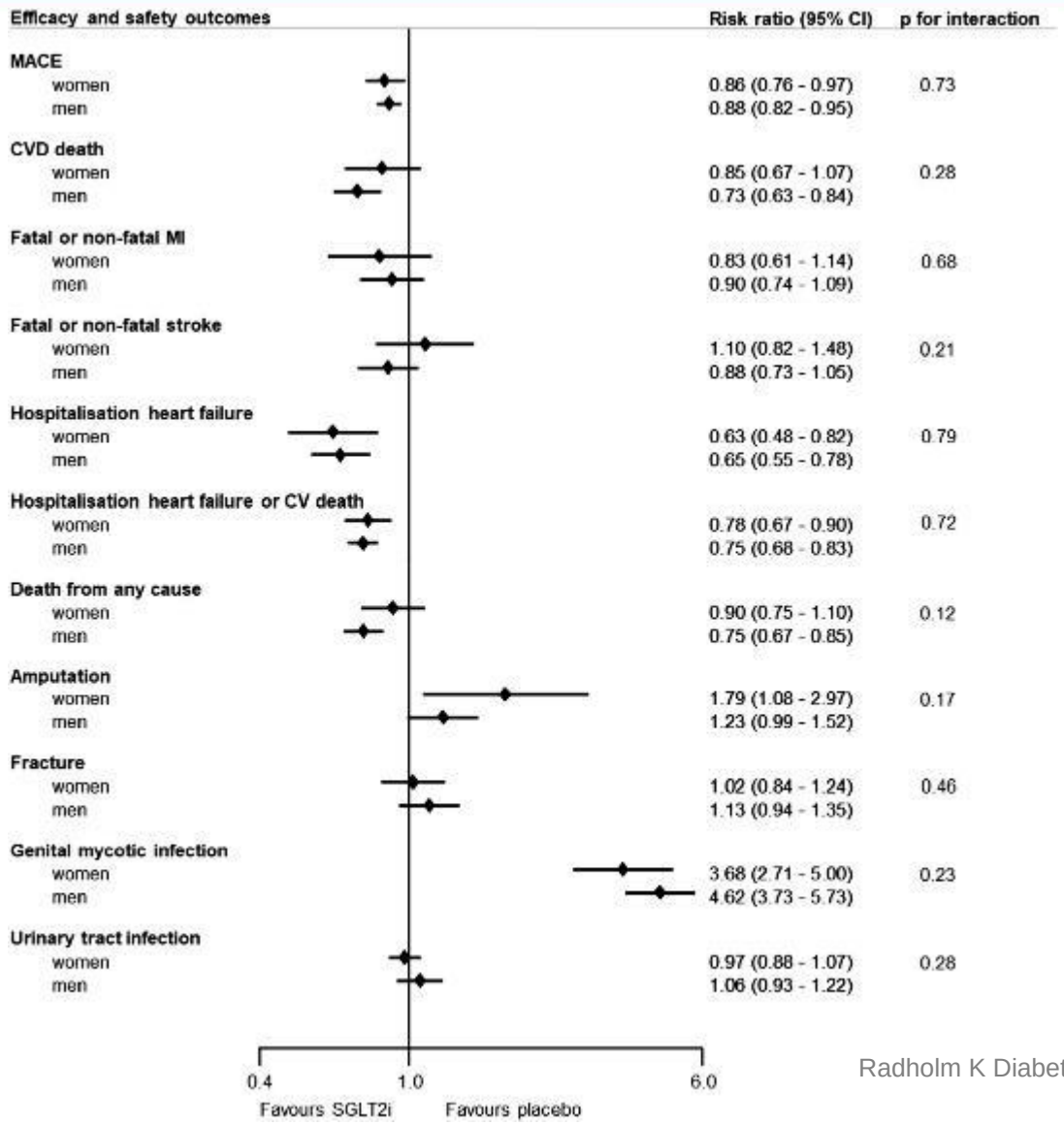
SGLT2i similar benefit & risks in Women and Men



- Pooled analysis of the EMPA REG OUTCOME trial, CANVAS Program, DECLARE-TIMI 58 trial and CREDENCE
- SGLT2 inhibition provided similar protection against vascular risks and death, and similar risks of serious adverse events, for women and men.
- Further, because the absolute risks of women and men included in these studies were only marginally different, there would be similarly large absolute benefits of therapy for both women and men.

Radholm K Diabetes, Obesity and Metabolism 2020 Feb;22(2):263-266. DOI: (10.1111/dom.13876)

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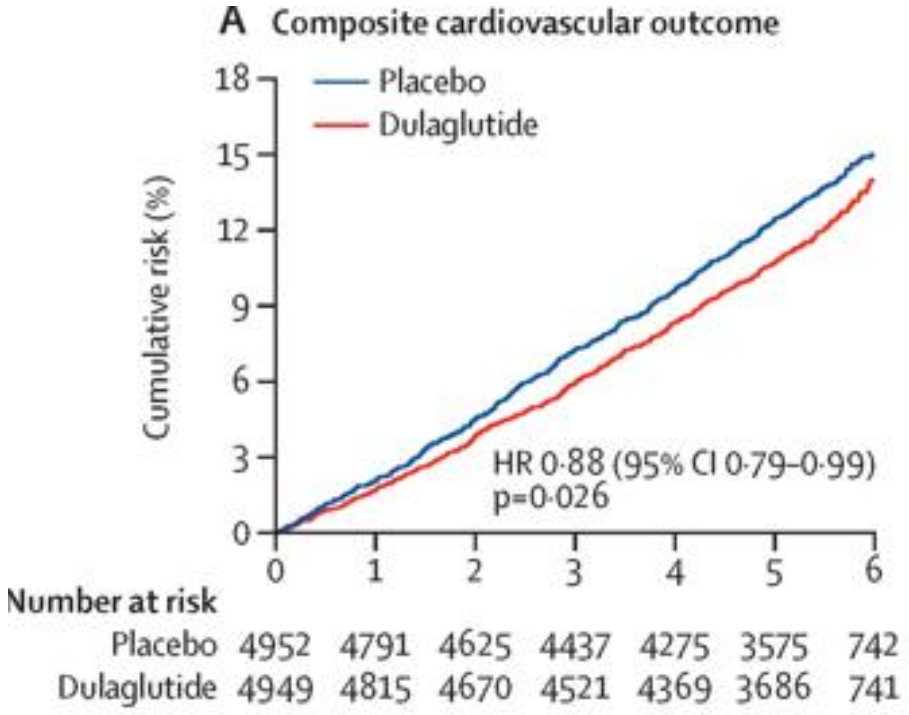
REWIND: Dulaglutide in Women and CV benefit

9901 participants; **4589 [46.3%] women**) were enrolled



	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person-years)	Events/patients (%)	Incidence (per 100 person-years)		
Age (years)						0·57
≥66	331/2314 (14·3%)	2·9	384/2350 (16·3%)	3·3	0·86 (0·74–1·00)	
<66	263/2635 (10·0%)	1·9	279/2602 (10·7%)	2·1	0·92 (0·78–1·09)	
Sex						0·60
Female	218/2306 (9·5%)	1·8	249/2283 (10·9%)	2·1	0·85 (0·71–1·02)	
Male	376/2643 (14·2%)	2·8	414/2669 (15·5%)	3·1	0·90 (0·79–1·04)	
Duration of diabetes (years)						0·88
<5	128/1227 (10·4%)	2·0	146/1192 (12·2%)	2·4	0·84 (0·66–1·06)	
5–10	174/1446 (12·0%)	2·3	196/1476 (13·3%)	2·6	0·89 (0·73–1·09)	
≥10	292/2276 (12·8%)	2·5	321/2284 (14·1%)	2·8	0·90 (0·77–1·06)	
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	
Baseline HbA_{1c}*						0·75
≥7·2%	328/2610 (12·6%)	2·5	373/2603 (14·3%)	2·9	0·86 (0·74–1·00)	
<7·2%	263/2329 (11·3%)	2·2	289/2334 (12·4%)	2·4	0·90 (0·76–1·06)	
BMI (kg/m^2)						0·21
≥32	254/2281 (11·1%)	2·1	308/2302 (13·4%)	2·6	0·82 (0·69–0·96)	
<32	340/2667 (12·7%)	2·5	355/2650 (13·4%)	2·7	0·94 (0·81–1·09)	
Region						0·0080
Europe	248/2174 (11·4%)	2·2	315/2165 (14·5%)	2·9	0·77 (0·65–0·90)	
Latin America	191/1511 (12·6%)	2·6	190/1510 (12·6%)	2·6	0·99 (0·81–1·21)	
USA and Canada	132/1032 (12·8%)	2·4	117/1039 (11·3%)	2·1	1·14 (0·89–1·47)	
Asia Pacific	23/232 (9·9%)	1·9	41/238 (17·2%)	3·5	0·54 (0·32–0·89)	
Overall	**594/4949 (12·0%)**	**2·4**	**663/4952 (13·4%)**	**2·7**	**0·88 (0·79–0·99)**	**NA**

Gerstein HC et alThe Lancet 2019 394121-130DOI: (10.1016/S0140-6736(19)31149-3)

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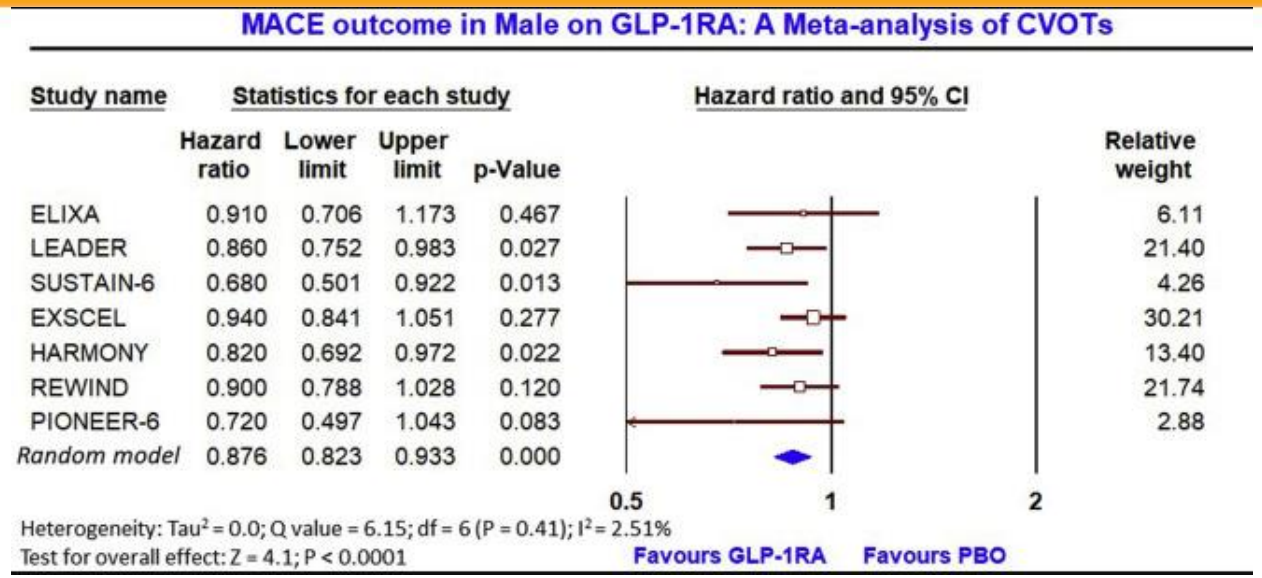
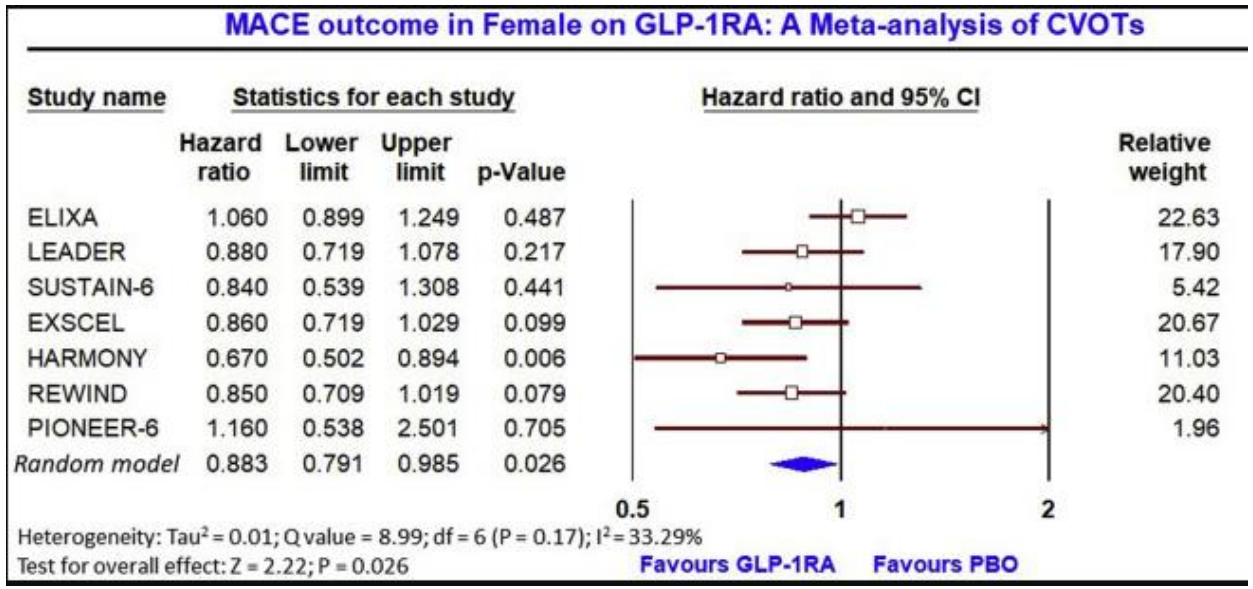
GLP1-RA in Women: Meta-analysis





- The meta-analysis of seven CVOTs conducted with GLP-1RAs (N = 56,004) demonstrated a significant reduction in MACE in both sex compared to placebo
  - Men - HR, 0.88; 95% CI, 0.82 to 0.93; P < 0.0001
  - Women - HR, 0.88; 95% CI, 0.79 to 0.99; P = 0.03)

Singh AK and Singh R. *Diabetes Metab Syndr*. 2020;14:181-187.

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Sex Differences in Cardiovascular Effectiveness of Newer Glucose-Lowering Drugs Added to Metformin in T2D

Marketscan Database 2011-2017

1st treatment of Sulfonylurea, SGLT-2i, GLP-1a, or DPP-4i
N = 2,547,972

↓

New User
N = 2,116,990

↓

Prior Metformin Use without prior use of insulin
N = 223,363

↓

Continuously enrolled 1 year prior to cohort entry
N = 180,311

↓

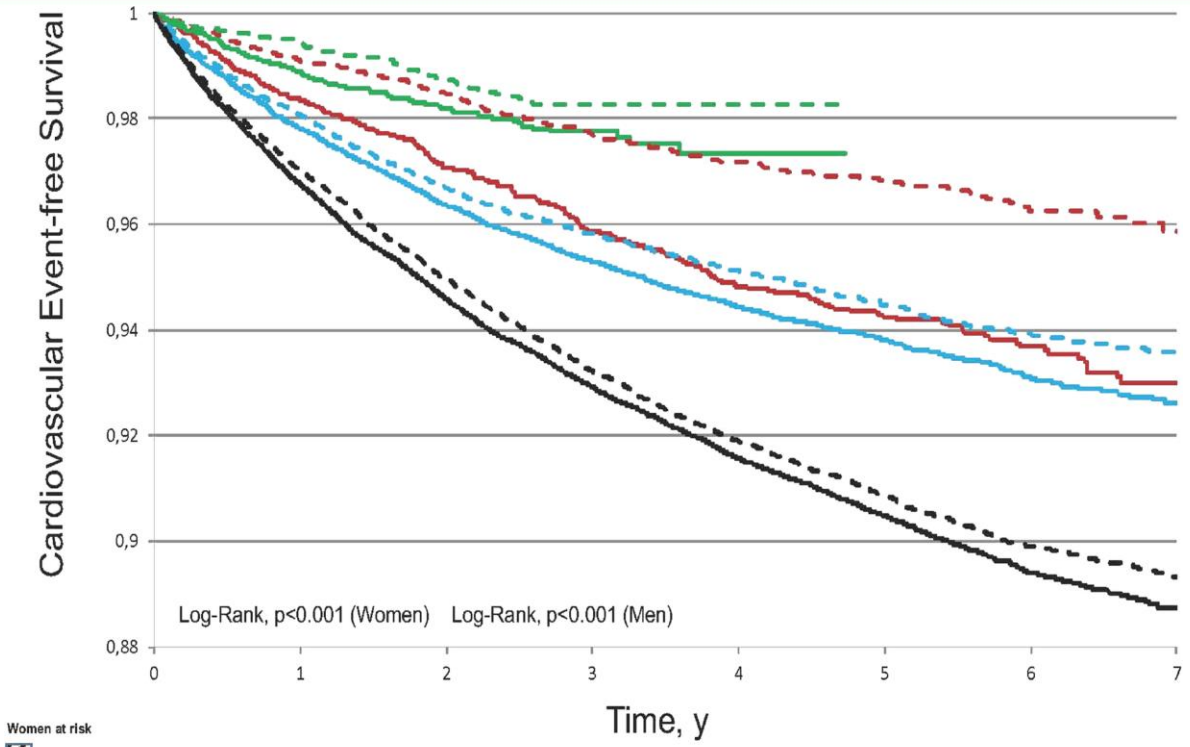
No gestational diabetes mellitus or cystic fibrosis
N =177,146

↓

At least 2 times criteria for type 2 diabetes
N = 167,341

↓

Final Cohort (Age >=18)
N = 167,254
(Men = 90,674; Women = 76,580)



Women at risk								
SU	38995	35503	32008	28691	24881	21001	15526	252
DPP-4i	23379	20945	18493	16232	13514	10739	6388	77
GLP-1RA	8755	7187	5894	4956	4159	3298	1985	13
SGLT-2i	5451	4030	2717	1268	191	0		

Men at risk								
SU	50110	45233	40474	36208	31050	25829	18806	298
DPP-4i	28299	25255	22346	19533	16047	12609	7337	86
GLP-1RA	5942	4777	3957	3359	2794	2212	1356	10
SGLT-2i	6323	4475	2861	1300	194	0		

Raparelli V et al. Sex Differences in Cardiovascular Effectiveness of Newer Glucose-Lowering Drugs Added to Metformin in Type 2 Diabetes Mellitus, JAHA 2020; 9(1)

Compared with sulfonylureas, hazard ratios (HRs) for cardiovascular events were lower with GLP-1RA (adjusted HR-women: 0.57, 95% CI: 0.48–0.68; aHR-men: 0.82, 0.71–0.95), dipeptidyl peptidase-4 inhibitors (aHR-women: 0.83, 0.77–0.89; aHR-men: 0.85, 0.79–0.91) and SGLT-2i (aHR-women: 0.58, 0.46–0.74; aHR-men: 0.69, 0.57–0.83). A sex-by-drug interaction was statistically significant only for GLP-1RA (*P*=0.002), suggesting greater cardiovascular effectiveness in women.

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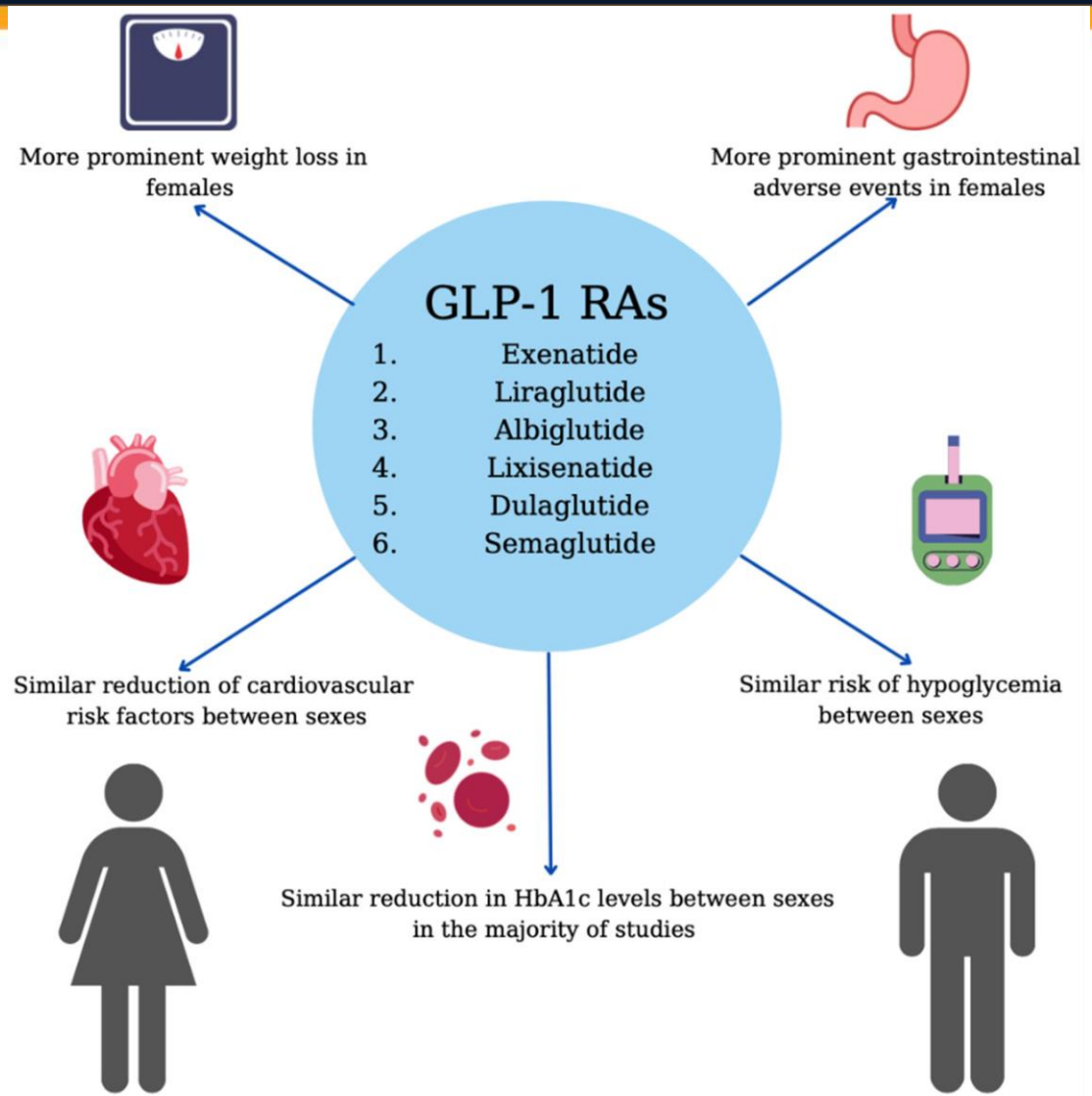
Sex Differences in Response to GLP1-RA



Rentzeperi E et al J. Pers. Med. 2022; 12(3), 454;

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Gestational Diabetes
A sex-specific CVD Risk

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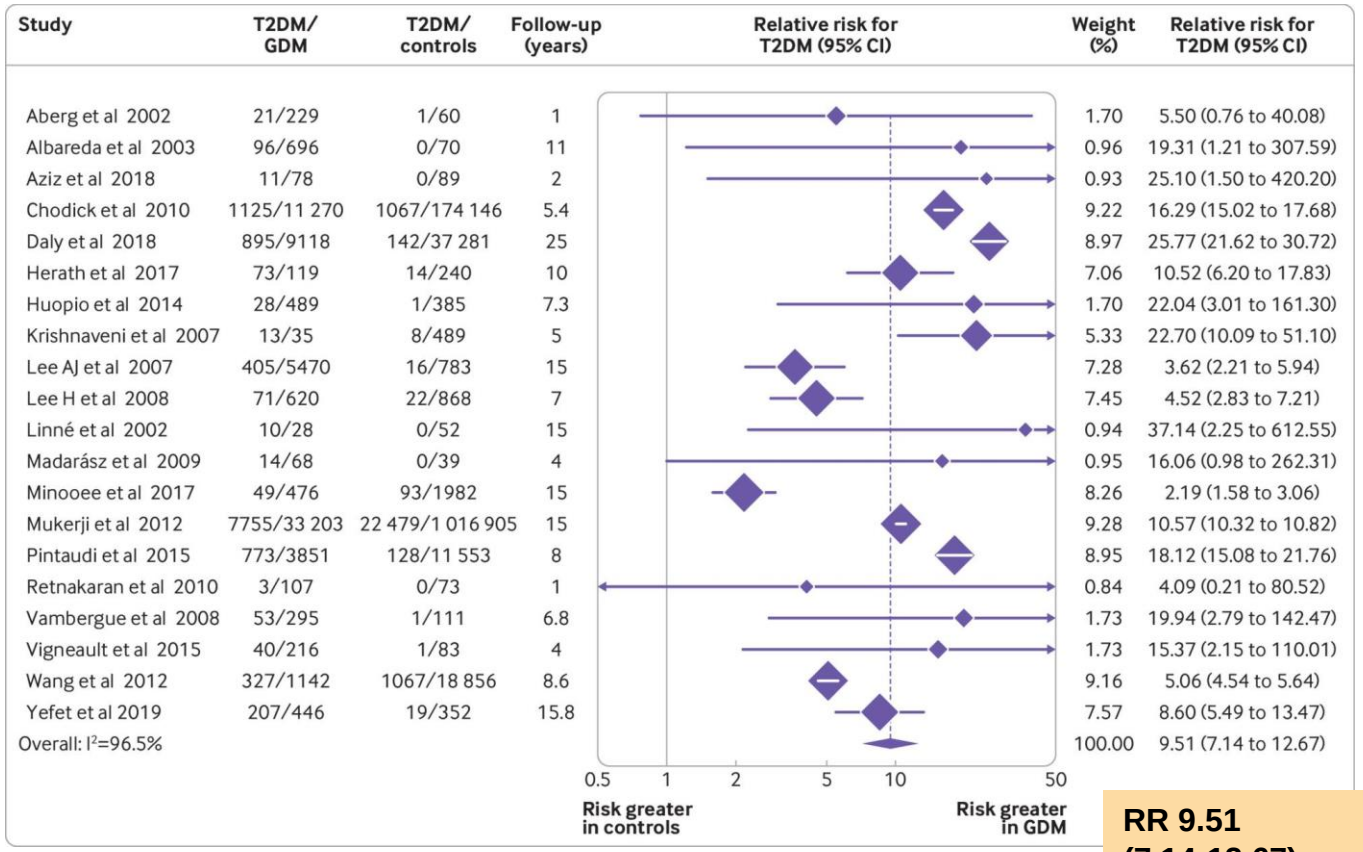
Gestational Diabetes Mellitus (GDM) and Risk of Type 2 Diabetes (T2D)

- **Gestational Diabetes**
  - 1 in 10 pregnancies
  - Up to 70% will develop T2D within 5 years

Relative risk of T2D in women with GDM compared with healthy controls



RR 9.51 (7.14-12.67)

Elpida Vounzoulaki et al. BMJ 2020;369:bmj.m1361

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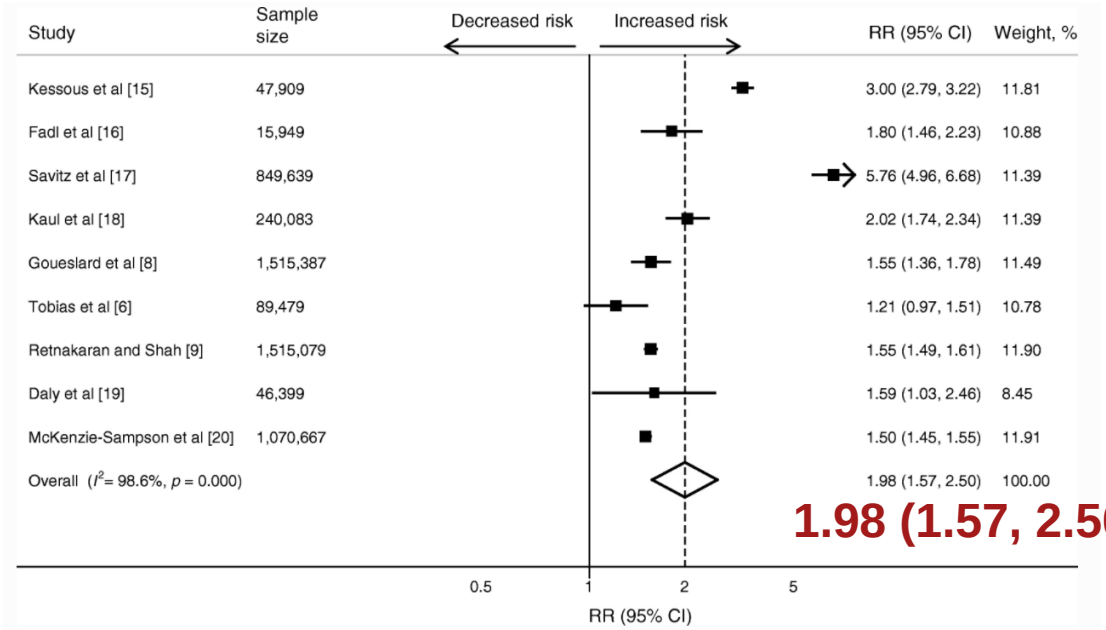
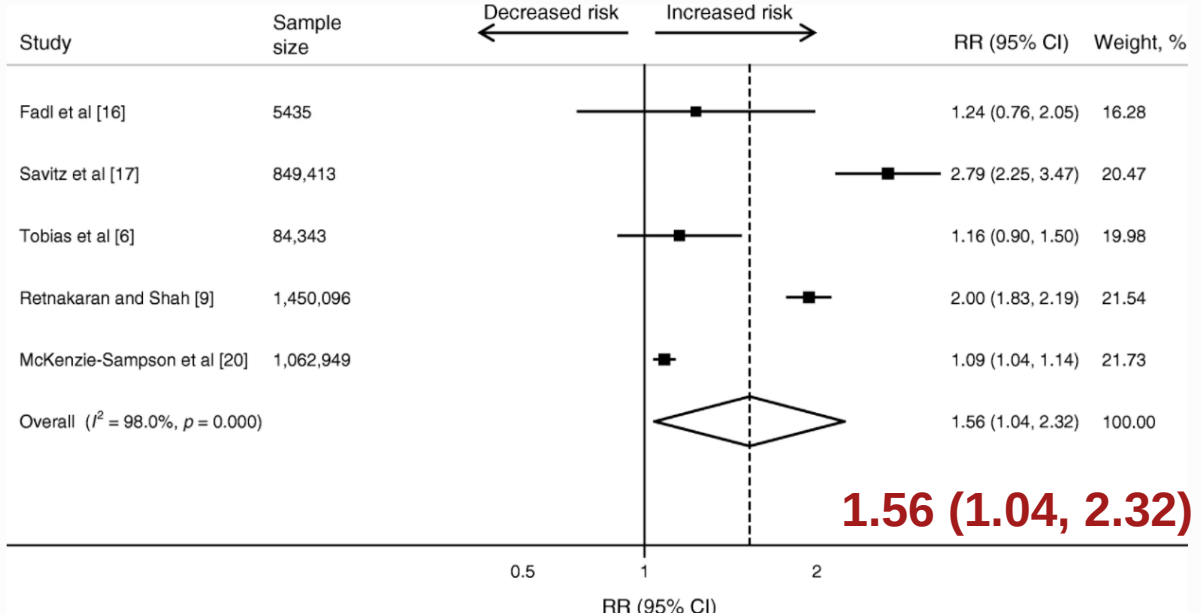
Gestational Diabetes Mellitus (GDM) and Risk of Maternal CVD

Meta-analysis of GDM and incident CVD



Meta-analysis of GDM and incident CVD among women who did NOT develop T2D



Kramer CK et al. Diabetologia 2019; 62: 905–914

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GDM and risk for incident HF and for PPCM

Administrative registry from Ontario, Canada with median followup of 7 years

Table 2—Event rates and relative risk (95% CI) for the association of gestational diabetes mellitus (GDM) and incident hospitalization for heart failure

	Crude incidence rate per 10,000 person-years (95% CI)	Hazard ratio (95% CI)		
		Unadjusted	Adjusted model 1	Adjusted model 2
No GDM	1.14 (1.05, 1.23)	1 (Reference)	1 (Reference)	1 (Reference)
GDM	2.58 (2.08, 3.20)	2.21 (1.76, 2.78)	1.62 (1.28, 2.05)	1.39 (1.09, 1.79)

Model 1: adjusted for age, ethnicity, neighborhood income quintile, rurality, parity, preterm delivery pregestational hypertension, preeclampsia, and preexisting cardiovascular disease. Model 2: model 1 plus chronic kidney disease, postpartum diabetes, postpartum hypertension, and postpartum coronary artery disease as time-varying covariates.

Table 3—OR (95% CI) for the association of gestational diabetes mellitus (GDM) and peripartum cardiomyopathy

Case subjects/number at risk		Odds ratio* (95% CI)	
		Unadjusted	Adjusted*
No GDM	502/848,202	1 (Reference)	1 (Reference)
GDM	83/49,662	2.83 (2.24, 3.57)	1.83 (1.45, 2.33)

*Adjusted for age, ethnicity, neighborhood income quintile, rurality, parity, preterm delivery (gestational age ≤36 weeks), pregestational hypertension, preeclampsia, and chronic kidney disease.

Echouffo-Tcheugui JB et al. Diabetes Care 2021;44:2346–2352 | https://doi.org/10.2337/dc21-0552

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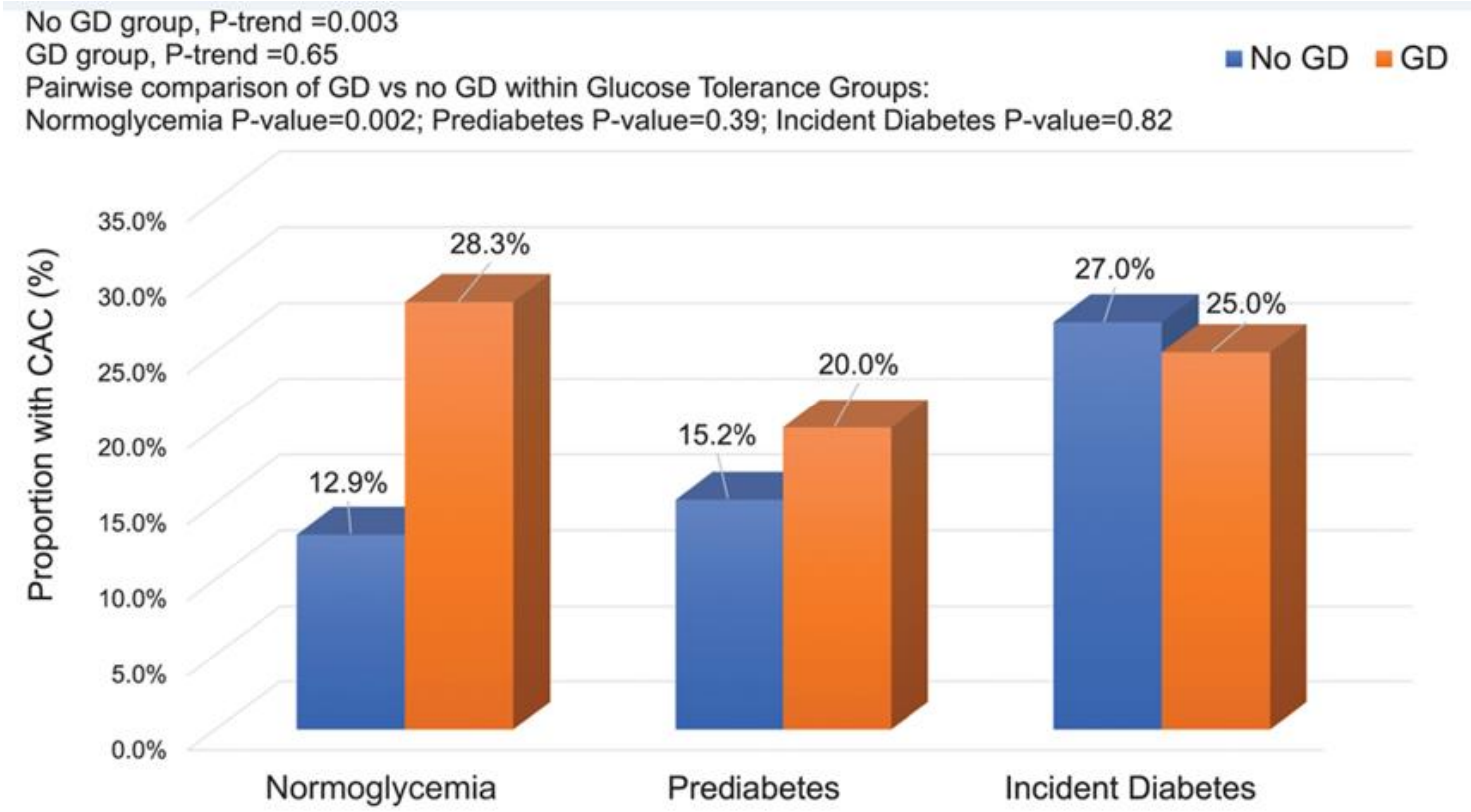
GDM history and risk of CAC 15 yrs later



Adjusted hazard ratios (95% CI) for CAC compared to no GDM/normoglycemia

- 1.54 (1.06–2.24) no GDM/prediabetes
- 2.17 (1.30–3.62) no GDM/incident DM
- 2.34 (1.34–4.09) GDM/normoglycemia
- 2.13 (1.09–4.17) GDM/prediabetes
- 2.02 (0.98–4.19) GDM/incident DM

Gunderson EP, et al. Circulation 2021

Concentric Remodeling and Reduced Diastolic & Endothelial Function among Women with history of GDM vs control

GDM Case (n=59) and Non-GDM Control (n=195) Women who underwent Echo & Endothelial Fxn Testing ~10yrs after index pregnancy

8-10 Years Postpartum

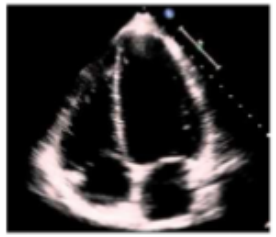
Mean age 38

GESTATIONAL DIABETES

DEFINITION
Glucose intolerance during pregnancy

RISK FACTORS
Obesity, advanced age, non-White, family history of T2DM

PREVALENCE
~10% in the US
~20% worldwide



Left ventricular structure/function

Echocardiogram
- ↑ Interventricular septal wall thickness
- ↑ Posterior wall thickness
- ↓ Septal e' velocity
- ↑ E/E' ratio
- ↑ Left ventricular mass
- ↑ Relative wall thickness (remodeling)

Vascular Endothelial Function

Peripheral Arterial Tonometry
- ↓ Reactive hyperemia index

Glycocalyx Analysis
- ↓ %Red blood cell filling
- ↑ Perfused boundary region 5-25, μm

American Heart Association. Go Red for women

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Minhas A.…Catov J, **Michos ED**. Circulation [abstract 2021]

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Conclusions: Sex specific impact of diabetes on ASCVD and Heart Failure

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Diabetes and CV Complications in Women

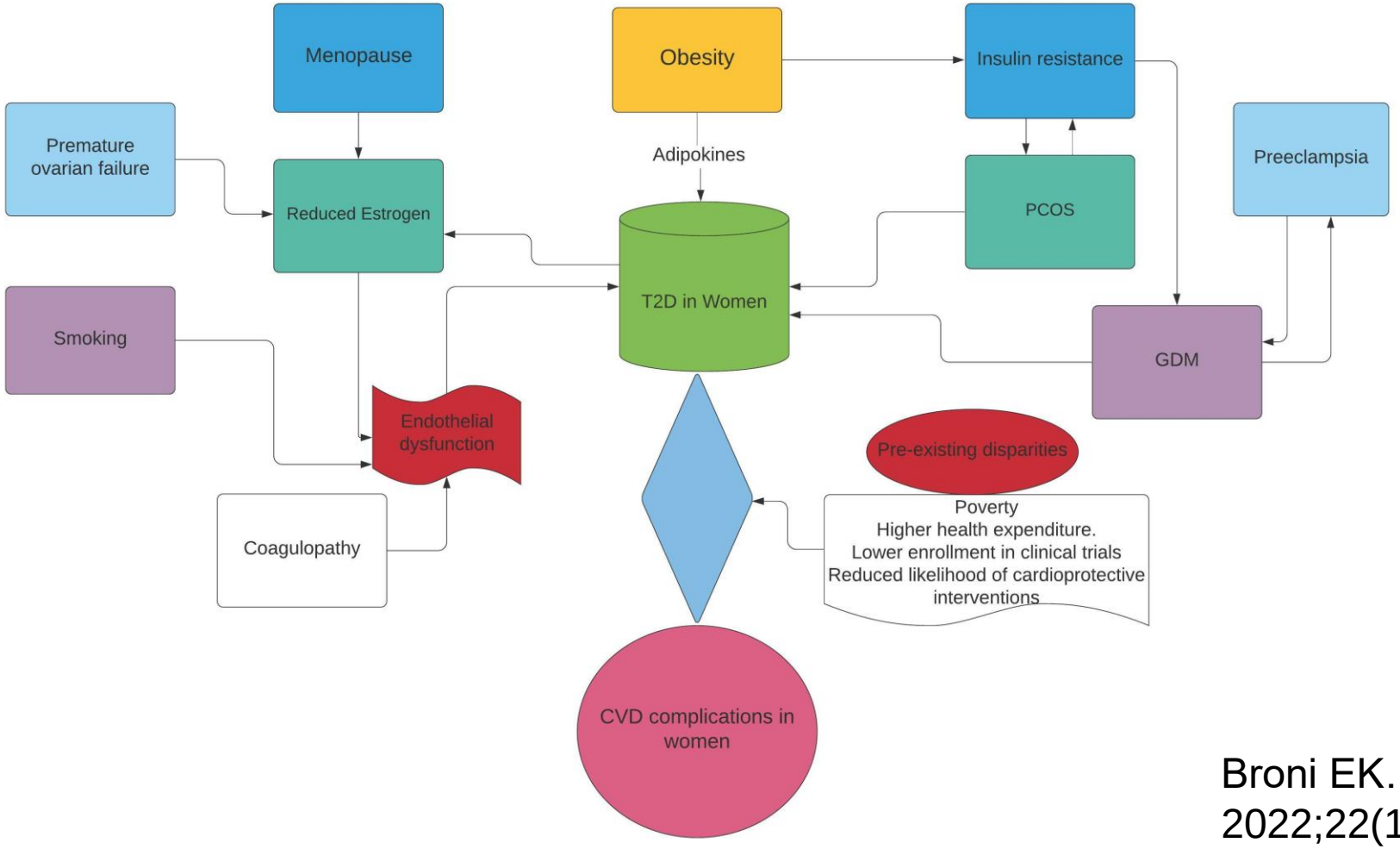

Figure 1: Interplay of risk factors, T2D and CVD complications in women. CVD; Cardiovascular Disease, PCOS;Polycystic Ovary Syndrome, T2D; Type 2 Diabetes , GDM; Gestational Diabetes melitus

Broni EK…**Michos ED**. Curr Diab Rep 2022;22(1):11-25

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Conclusions

- Men have a greater prevalence of diabetes and of CVD.
- However, diabetes status confers a greater relative risk for coronary heart disease, stroke, vascular dementia, and heart failure in women compared to men
- Women with T2D have been underrepresented in most clinical trials (lipid lowering therapies, new anti-diabetes drugs, etc) which limits firm conclusions about efficacy & safety of many drug treatments in women with T2D
- Women with T2D may experience greater benefits than men from GLP-1 receptor agonists.

Conclusions:

- Compared to men, women have higher BMI and more adverse cardiovascular risk profile at time of diabetes diagnosis
- LDL-C & BP less well controlled in women with diabetes.
- Women less likely to be treated with statins
- Female-specific risk factors of polycystic ovary syndrome (PCOS) and the adverse pregnancy outcomes of gestational diabetes and pre-eclampsia are associated with future T2D and CVD in women
- Intensified & optimized control of RFs is needed in women with diabetes