Diabete e Gender

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E GERIATRIA

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Relevant Finacial Disclosures

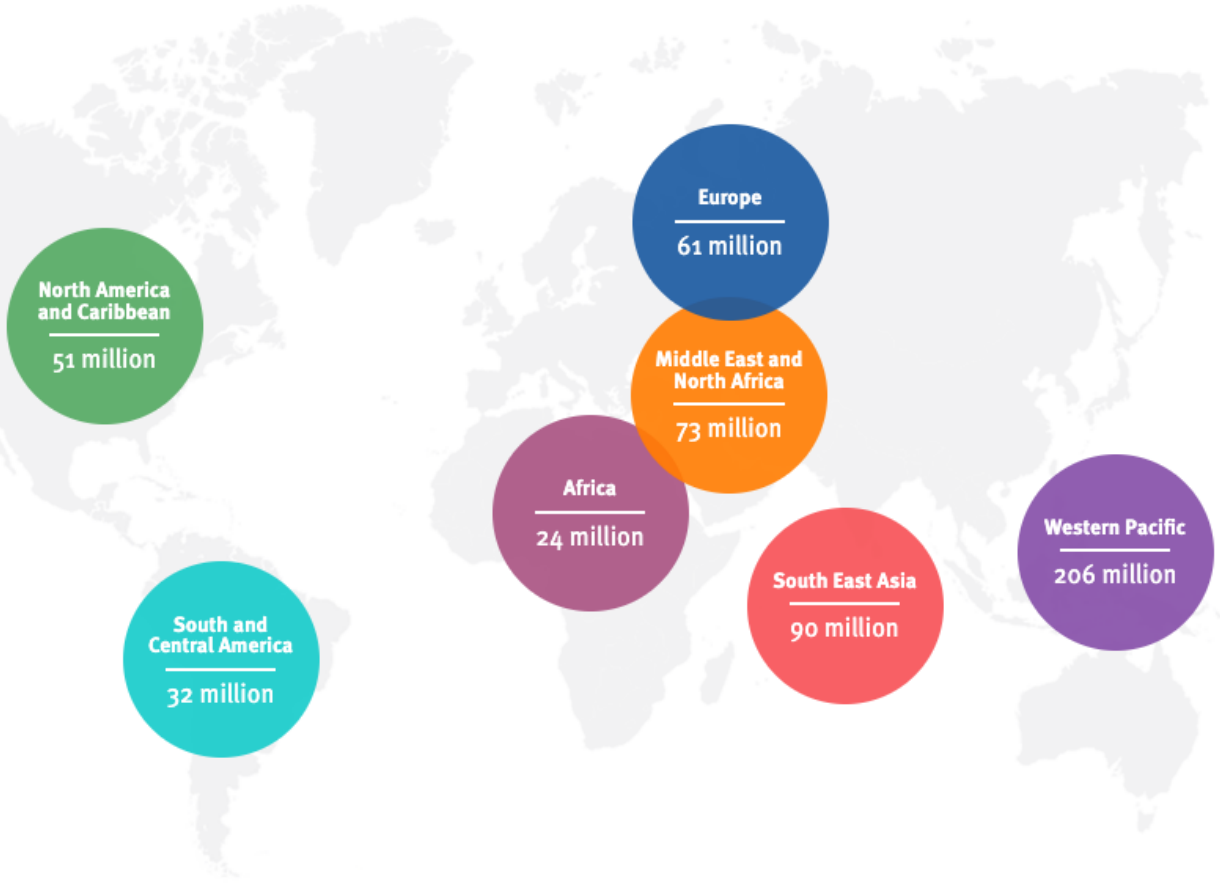
As Speaker , Advisory Board , and Consultant in the last 3 years :

Amarin

Novo-Nordisk

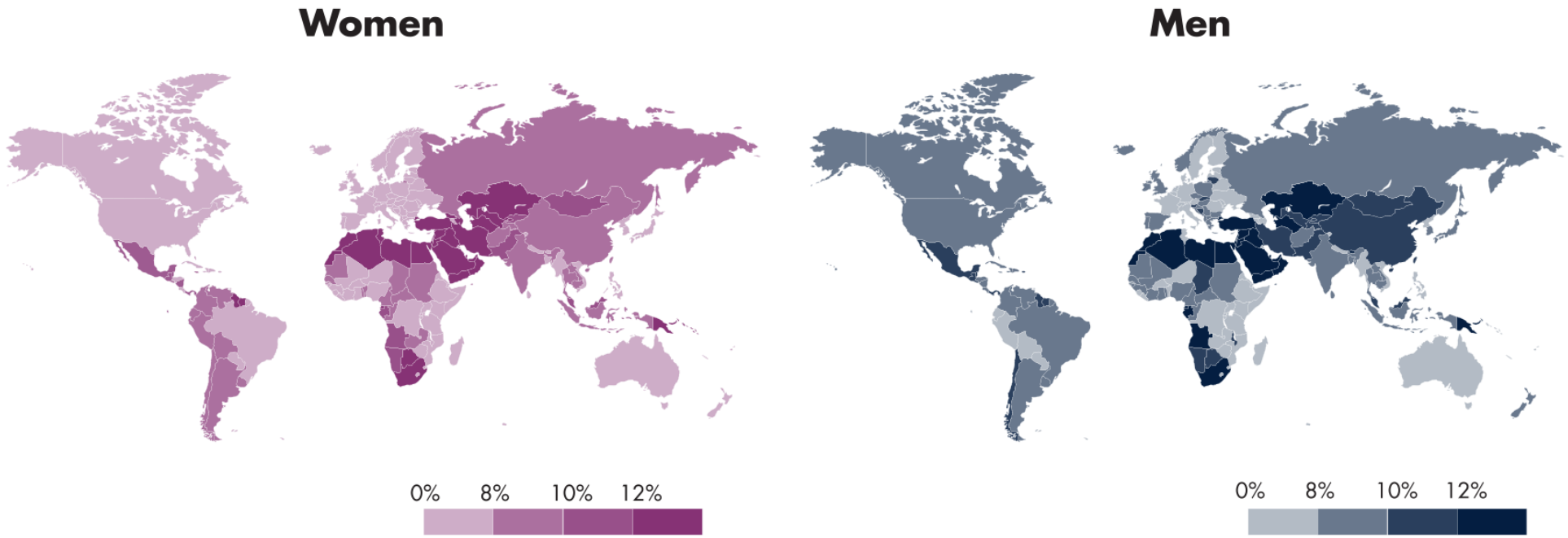
Eli-Lilly

Diabetes around the world in 2021

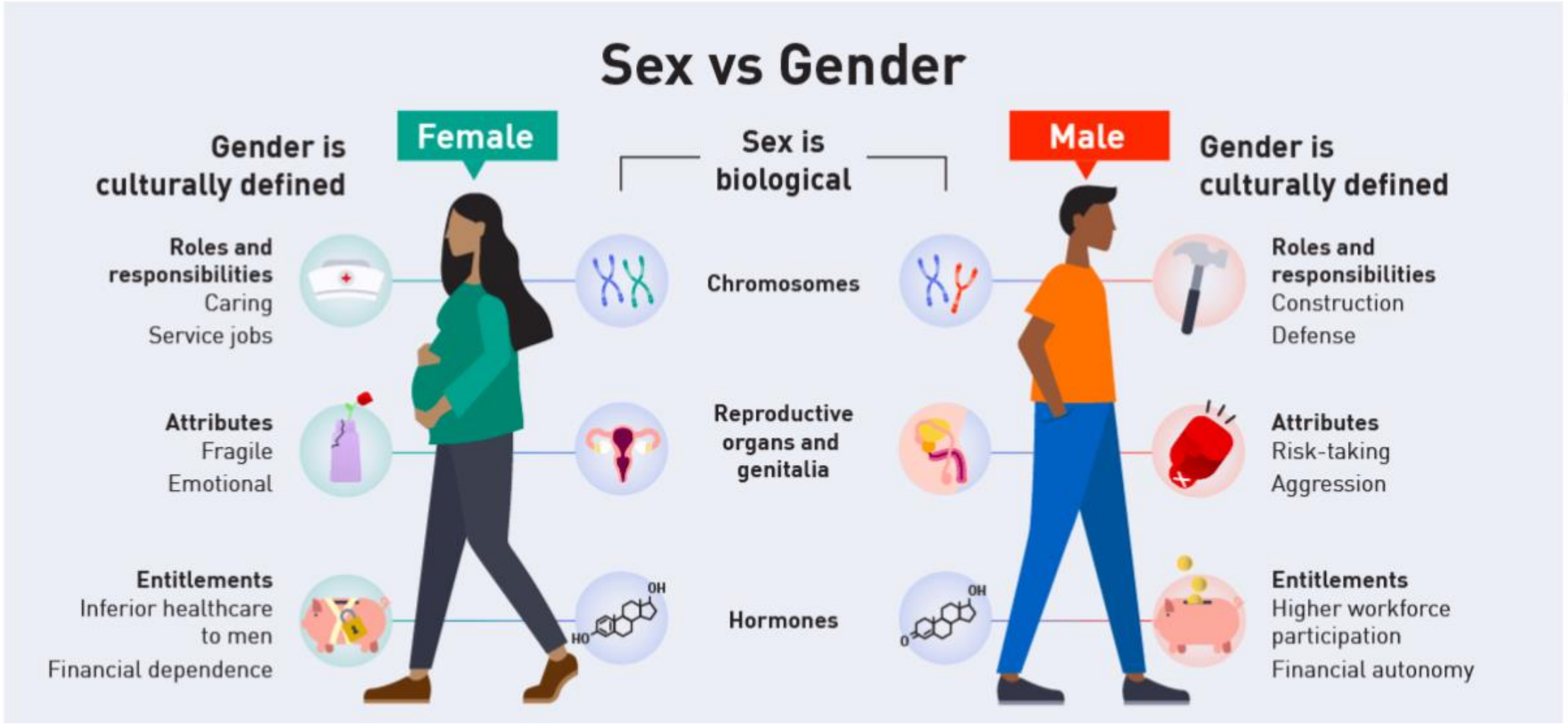


International Diabetes Federation, Diabetes Atlas 10th Edition, 2019

Diabetes prevalence in woman and men

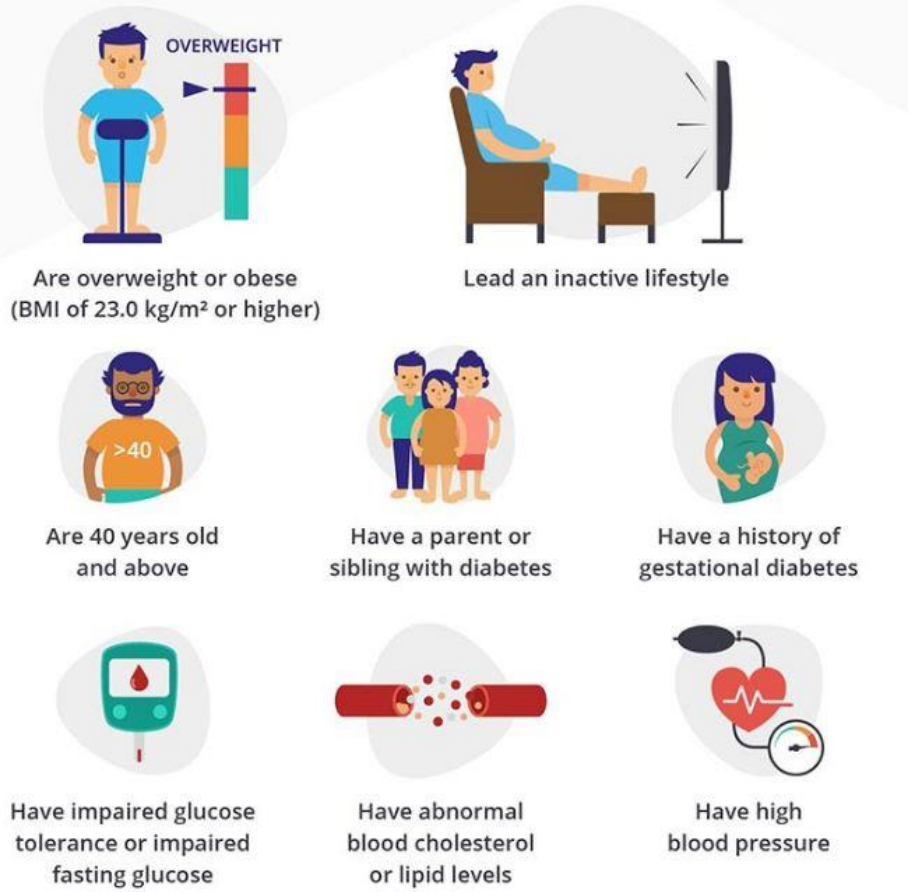


Endocr Rev, Volume 37, 9 May 2016 Page 278-316 doi: 10.1210/er.2015-1137.

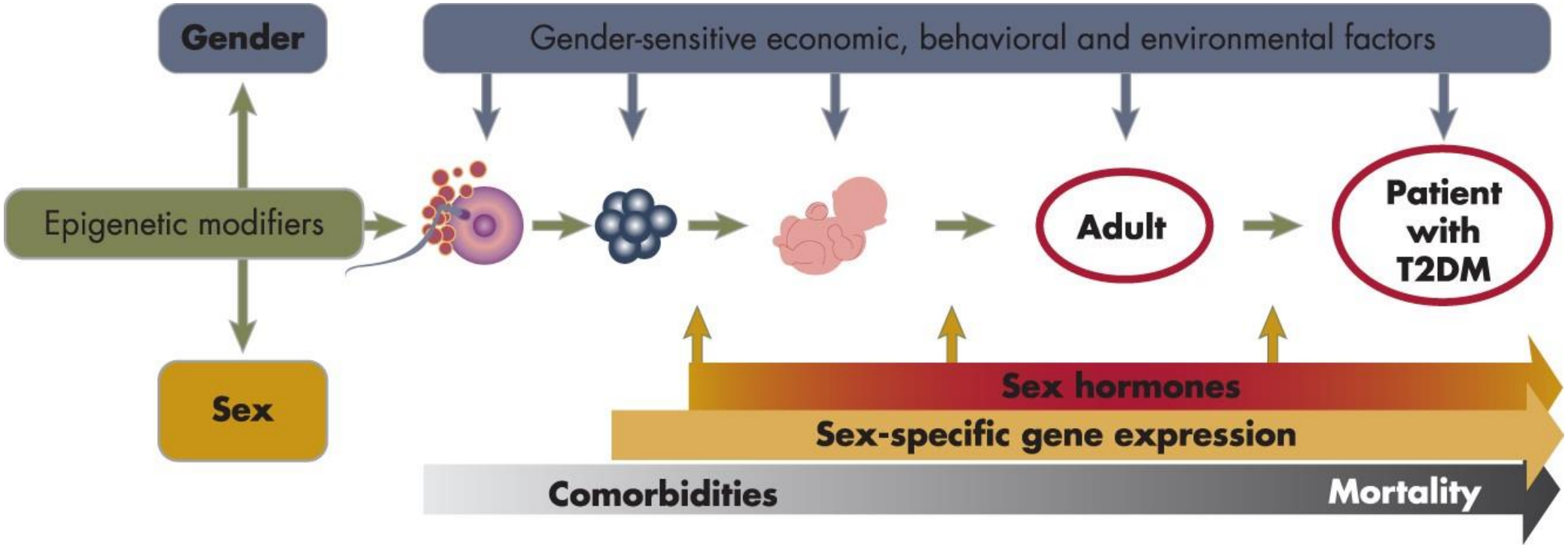


Lancet Series on Gender Equality, Norms and Health, Paper 1, 2019

- **Biological risk factors**
- Psychological risk factors
- Genetic predisposition
- Diabetes complications
- Antidiabetic Agent



Lifelong impact and interaction between sex and gender on development and outcomes of Type 2 Diabetes Mellitus (T2D)



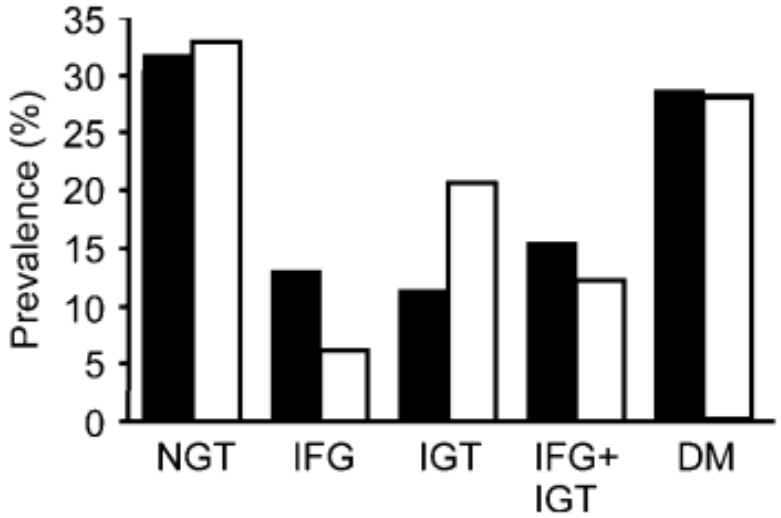
Endocr Rev, Volume 37, 9 May 2016 Page 278-316 doi: 10.1210/er.2015-1137.

Sex and prevalence of impaired fasting glucose, impaired glucose tolerance and T2DM

American Diabetes Association.

- AusDiabStudy
- Inter99 Study
- GENNID Study Group

Isolated IFG was more frequent in men (13.1 vs. 6.2%), whereas isolated IGT was more frequent in women (20.7 vs. 11.3%).

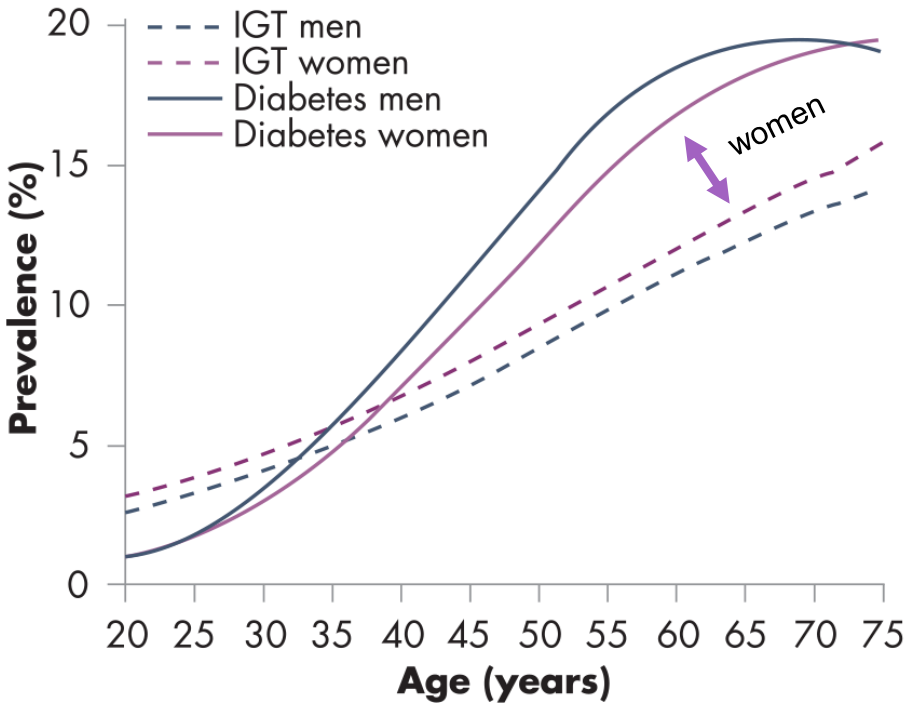


■ 835 men □ 1329 women

Diabetes. Volume 55, December 2006, Pages 3529-35. doi: 10.2337/db06-0577.

Prevalence of prediabetes and diabetes in women

ENDOCRINE SOCIETY



Women show an acceleration of developing diabetes after menopause

Endocr Rev., Volume 37, 9 May 2016, Pages 278-316. doi: 10.1210/er.2015-1137.

The associations of menopausal age and reproductive life span (menopausal age minus menarcheal age) with diabetes risk: results from the EPIC-INTERACT STUDY

American Diabetes Association.

		HR (95% CI)			
	N total/cases	Crude	Model 1	Model 2	Model 3
Menopausal age (years)					
<40	419/220	1.50 (1.22–1.85)	1.50 (1.22–1.85)	1.28 (1.00–1.64)	1.32 (1.04–1.69)
40–44	887/424	1.19 (1.02–1.38)	1.18 (1.02–1.37)	1.08 (0.89–1.30)	1.09 (0.90–1.31)
45–49	2,570/1,186	1.05 (0.95–1.17)	1.05 (0.95–1.17)	0.97 (0.86–1.10)	0.97 (0.86–1.10)
50–54	3,333/1,554	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)
≥55	655/307	0.91 (0.77–1.08)	0.92 (0.77–1.08)	0.84 (0.69–1.02)	0.85 (0.70–1.03)
Menopausal age (per SD decrease)	7,864/3,691	1.11 (1.06–1.16)	1.11 (1.06–1.16)	1.07 (1.01–1.13)	1.08 (1.02–1.14)
Reproductive life span (years)					
Quartile 1 (<33)	1,982/959	1.11 (0.97–1.28)	1.11 (0.97–1.28)	1.16 (0.97–1.38)	1.17 (0.98–1.39)
Quartile 2 (33–36)	2,364/1,077	0.94 (0.82–1.08)	0.94 (0.82–1.08)	1.00 (0.85–1.19)	1.00 (0.85–1.19)
Quartile 3 (37–39)	1,979/897	0.91 (0.79–1.04)	0.91 (0.79–1.04)	0.97 (0.82–1.14)	0.96 (0.82–1.14)
Quartile 4 (≥40)	1,443/710	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)
Reproductive life span (per SD decrease)	7,768/3,643	1.07 (1.02–1.12)	1.07 (1.02–1.12)	1.06 (1.00–1.12)	1.06 (1.01–1.12)

Diabetes Care. Volume 36, 10 December 2012, Pages 1012-9. doi: 10.2337/dc12-1020.

Testosterone deficiency and T2DM in men

American Diabetes Association.

Endogenous Sex Hormones and the Development of Type 2 Diabetes in Older Men and Women: the RANCHO BERNARDO STUDY

		Men		Women	
Independent variables†	Covariates†	β	*P*	β	*P*
Testosterone	Model 1	−0.37	0.001	−0.023	0.71
	Model 2	−0.24	0.02	0.020	0.76
	Model 3	−0.31	0.02	0.011	0.88
Bioavailable testosterone	Model 1	−0.10	0.39	0.15	0.003
	Model 2	−0.13	0.23	0.15	0.01
	Model 3	−0.15	0.28	0.15	0.02
Estradiol	Model 1	−0.13	0.24	0.035	0.61
	Model 2	−0.08	0.47	0.054	0.49
	Model 3	−0.05	0.64	0.025	0.77
Bioavailable estradiol	Model 1	−0.03	0.79	0.14	0.01
	Model 2	−0.07	0.49	0.15	0.02
	Model 3	−0.05	0.66	0.14	0.055

Diabetes Care. January 2002, Volume 25 Pages 55-60. doi: 10.2337/diacare.25.1.55..

Testosterone excess and T2DM in women

Diabetologia

Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study

Analysis	Oestradiol[a]		Free oestradiol [b]		Testosterone[c]		Free testosterone[d]	
	RR (95% CI)	*p* value for trend	RR (95% CI)	*p* value for trend	RR (95% CI)	*p* value for trend	RR (95% CI)	*p* value for trend
Multivariate	1.97 (1.28–3.04)	0.002	2.78 (1.89–4.10)	<0.001	1.48 (1.01–2.17)	0.05	2.30 (1.60–3.30)	<0.001
Multivariate (excluding first 3 years follow-up)	1.88 (1.09–3.25)	0.02	2.97 (1.82–4.85)	<0.001	1.46 (0.92–2.34)	0.11	2.60 (1.63–4.14)	<0.001
Multivariate +HDL + TG[e]	2.08 (0.93–4.65)	0.07	2.91 (1.47–5.73)	0.002	1.72 (0.92–3.20)	0.09	2.38 (1.14–4.97)	0.02
Multivariate + waist circumference	1.80 (1.15–2.83)	0.01	2.55 (1.72–3.78)	<0.001	1.43 (0.93–2.20)	0.11	2.14 (1.48–3.10)	<0.001
Multivariate + C-reactive protein	2.25 (1.39–3.66)	0.001	2.70 (1.78–4.10)	<0.001	1.33 (0.88–2.02)	0.18	1.99 (1.31–3.03)	0.001
Multivariate (among those with HbA_{1c} <6%)	2.00 (1.18–3.36)	0.009	3.07 (1.85–5.09)	<0.001	1.39 (0.86–2.24)	0.17	2.40 (1.49–3.88)	<0.001

Results

In PostMenopausal women, higher plasma levels of oestradiol and testosterone were strongly and prospectively related to increased risk of developing type 2 diabetes.

Diabetologia. Volume 50, !4 august 2007 Pages :2076-84. doi: 10.1007/s00125-007-0785-y.

Gestational Diabetes and T2DM

Persistence of Risk for Type 2 Diabetes After Gestational Diabetes Mellitus

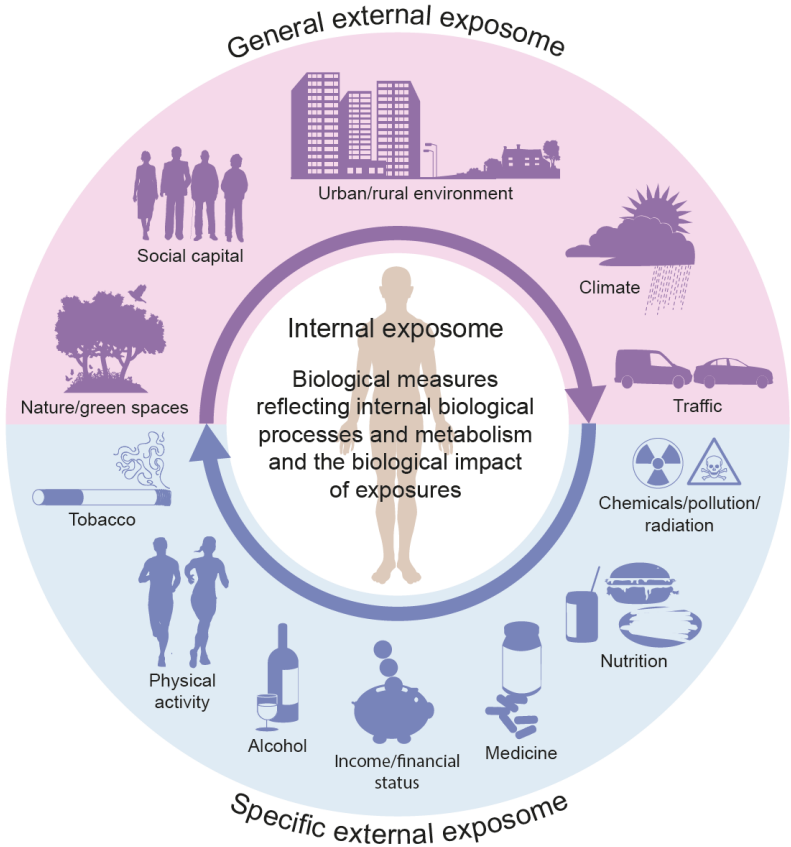
Conclusions

Gestational diabetes mellitus predicted markedly increased rates of type 2 diabetes.

	Ever having pregnancy with GDM, HR (95% CI)		Time since last pregnancy with GDM, HR (95% CI)
	No GDM	GDM	
Person-years	462,042	10,958	—
Participants, *n*	45,357	1,172	—
Model 1: model with no time since GDM interaction	1 (ref)	2.50 (2.15–2.91)	—
Model 2: model with time since GDM interaction term†			
GDM effect†	1 (ref)	5.07 (3.36–7.65)	0.76 (0.66–0.88)
Model 3: model stratified by time since last pregnancy with GDM, years			
6–15	1 (ref)	3.87 (2.60–5.75)	—
16–25	1 (ref)	3.50 (2.79–4.40)	—
26–35	1 (ref)	1.95 (1.46–2.61)	—
>35	1 (ref)	1.62 (1.12–2.33)	—

Diabetes Care 2022;45:864–870, https://doi.org/10.2337/dc21-1430.

- Biological risk factors
- **Psychological risk factors**
- Genetic predisposition
- Diabetes complications
- Antidiabetic Agent



Diabetologia 2021, DOI 10.1007/s00125-021-05618-w

Work stress and T2DM

Obesity

Work Stress, Obesity and the Risk of Type 2 Diabetes: Gender-Specific Bidirectional Effect in the Whitehall II Study

Among women, work stress was associated with higher risk of T2DM in the obese (HR 2.01: 1.06; 3.92) but not in the nonobese ($P_{INTERACTION}$ = 0.005)

All men		Nonobese men (BMI <30 kg/m²)		Obese men (BMI ≥30 kg/m²)		
Cases/total	HR (95% CI)	Cases/total	HR (95% CI)	Cases/total	HR (95% CI)	*P* for interaction[a]
389/3,689	0.80 (0.63; 1.02)	310/3,429	0.70 (0.53; 0.93)	79/260	1.05 (0.63; 1.75)	0.17
All women		**Nonobese women (BMI <30 kg/m²)**		**Obese women (BMI ≥30 kg/m²)**		
Cases/total	HR (95% CI)	Cases/total	HR (95% CI)	Cases/total	HR (95% CI)	*P* for interaction[a]
151/1,449	1.37 (0.98; 1.92)	104/1,248	1.18 (0.63; 2.10)	47/201	2.01 (1.06; 3.82)	0.005

Obesity (Silver Spring). Volume 20, February 2012, Pages 428-33. doi: 10.1038/oby.2011.95.

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GENETIC PREDISPOSITION

Sexual dimorphism in genetic predisposition

Fetal sex influences gene expression and produces functional differences in the human placentas that increase the susceptibility to developing type 2 diabetes in the offspring.

						Sex-combined			Women			Men			Sex diff.
SNP	Trait	Chr	Locus	EA*	EAF	β	*P*	*N*	β	*P*	*N*	β	*P*	*N*	*P*†
Loci achieving genome-wide significance in European-ancestry meta-analyses															
rs10925060	WCadjBMI	1	*OR2W5-NLRP3*	T	0.03	0.017	2.2×10^{-5}	140,515	0.002	6.8×10^{-1}	85,186	0.045	$\mathbf{9.1\times10^{-13}}$	55,522	$\mathbf{1.7\times10^{-8}}$
rs10929925	HIP	2	*SOX11*	C	0.55	0.020	$\mathbf{4.5\times10^{-8}}$	207,648	0.021	9.0×10^{-6}	115,428	0.018	3.2×10^{-4}	92,499	6.1×10^{-1}
rs2124969	WCadjBMI	2	*ITGB6*	C	0.42	0.020	$\mathbf{7.1\times10^{-9}}$	231,284	0.016	3.5×10^{-4}	127,437	0.025	2.3×10^{-7}	104,039	1.4×10^{-1}
rs17472426	WCadjBMI	5	*CCNJL*	T	0.92	0.014	3.1×10^{-2}	217,564	−0.014	1.0×10^{-1}	119,804	0.052	$\mathbf{4.3\times10^{-8}}$	97,954	$\mathbf{3.9\times10^{-8}}$
rs7739232	HIPadjBMI	6	*KLHL31*	A	0.07	0.037	5.4×10^{-5}	131,877	0.063	$\mathbf{1.0\times10^{-8}}$	80,475	−0.004	7.5×10^{-1}	51,589	$\mathbf{2.9\times10^{-5}}$
rs13241538	HIPadjBMI	7	*KLF14*	C	0.48	0.017	1.6×10^{-6}	210,935	0.033	$\mathbf{9.9\times10^{-14}}$	117,210	−0.003	5.0×10^{-1}	93,911	$\mathbf{2.0\times10^{-9}}$
rs7044106	HIPadjBMI	9	*C5*	C	0.24	0.023	4.1×10^{-5}	143,412	0.039	$\mathbf{5.7\times10^{-9}}$	86,733	−0.003	6.9×10^{-1}	56,865	$\mathbf{1.3\times10^{-5}}$
rs11607976	HIP	11	*MYEOV*	C	0.70	0.022	$\mathbf{4.2\times10^{-8}}$	212,815	0.019	1.9×10^{-4}	118,391	0.024	7.7×10^{-6}	94,701	4.4×10^{-1}
rs1784203	WCadjBMI	11	*KIAA1731*	A	0.01	0.031	1.3×10^{-8}	63,892	0.000	9.9×10^{-1}	35,539	0.075	$\mathbf{1.0\times10^{-19}}$	28,353	1.2×10^{-1}
rs1394461	WHR	11	*CNTN5*	C	0.25	0.017	4.7×10^{-4}	144,349	0.035	$\mathbf{3.6\times10^{-8}}$	87,441	−0.011	1.6×10^{-1}	57,094	$\mathbf{1.1\times10^{-6}}$
rs319564	WHR	13	*GPC6*	C	0.45	0.014	3.4×10^{-5}	212,137	0.003	5.3E-01	117,970	0.027	$\mathbf{1.6\times10^{-8}}$	94,350	$\mathbf{6.0\times10^{-5}}$
rs2047937	WCadjBMI	16	*ZNF423*	C	0.50	0.019	$\mathbf{4.7\times10^{-8}}$	231,009	0.022	5.5×10^{-7}	127,288	0.014	3.6×10^{-3}	103,914	2.0×10^{-1}
rs2034088	HIPadjBMI	17	*VPS53*	T	0.53	0.021	4.8×10^{-9}	210,737	0.028	$\mathbf{9.6\times10^{-10}}$	117,142	0.014	6.5×10^{-3}	93,781	2.5×10^{-2}
rs1053593	HIPadjBMI	22	*HMGXB4*	T	0.65	0.021	3.9×10^{-8}	202,070	0.029	$\mathbf{1.8\times10^{-9}}$	114,347	0.011	5.1×10^{-2}	87,908	6.2×10^{-3}
Loci achieving genome-wide significance in all-ancestry meta-analyses															
rs1664789	WCadjBMI	5	*ARL15*	C	0.41	0.014	2.6×10^{-5}	244,110	0.005	2.8×10^{-1}	133,052	0.026	$\mathbf{3.6\times10^{-8}}$	109,025	$\mathbf{4.4\times10^{-4}}$
rs722585	HIPadjBMI	6	*GMDS*	G	0.68	0.015	2.1×10^{-4}	205,815	−0.001	8.8×10^{-1}	113,965	0.032	$\mathbf{9.2\times10^{-9}}$	89,831	$\mathbf{4.3\times10^{-6}}$
rs1144	WCadjBMI	7	*SRPK2*	C	0.34	0.019	$\mathbf{3.1\times10^{-8}}$	239,342	0.020	1.2×10^{-5}	131,398	0.018	4.1×10^{-4}	105,911	7.8×10^{-1}
rs2398893	WHR	9	*PTPDC1*	A	0.71	0.020	$\mathbf{4.0\times10^{-8}}$	226,572	0.019	5.1×10^{-5}	124,577	0.019	2.7×10^{-4}	99,968	9.5×10^{-1}
rs4985155‡	HIP	16	*PDXDC1*	A	0.66	0.018	4.5×10^{-7}	227,296	0.011	1.6×10^{-2}	125,048	0.029	$\mathbf{9.7\times10^{-9}}$	100,313	6.3×10^{-3}

Results:

Sex-specific differences were found in genetic loci, which are involved in regulatory functions of adipose tissue and insulin biology

Nature. 2015 Feb 12;518(7538):187-196. doi: 10.1038/nature14132.

- Biological risk factors
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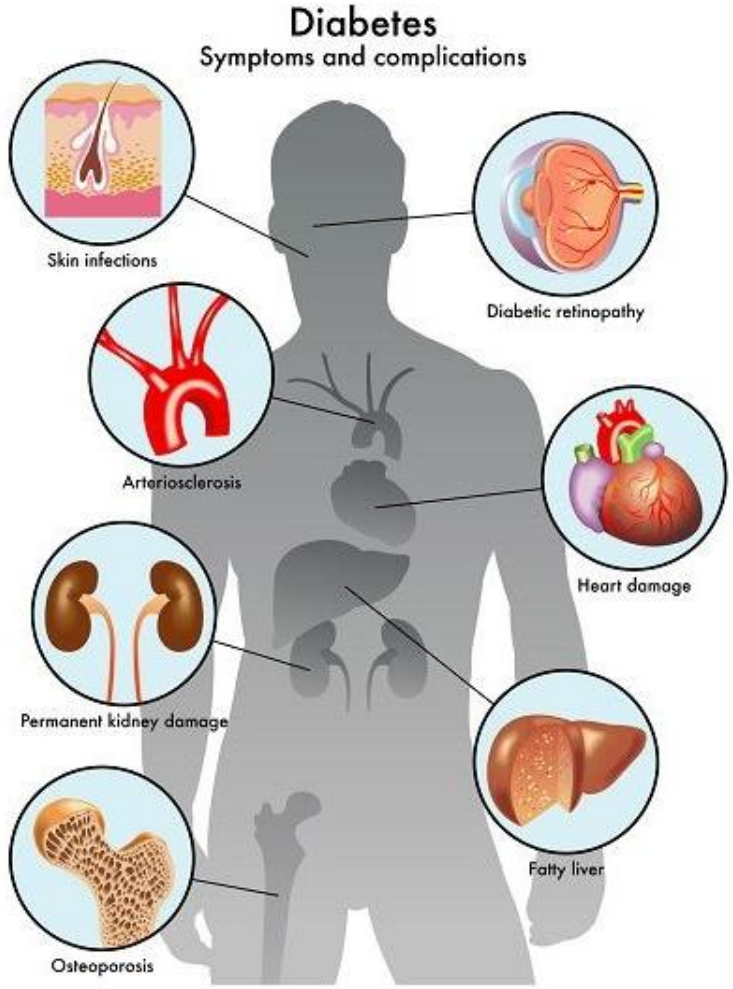
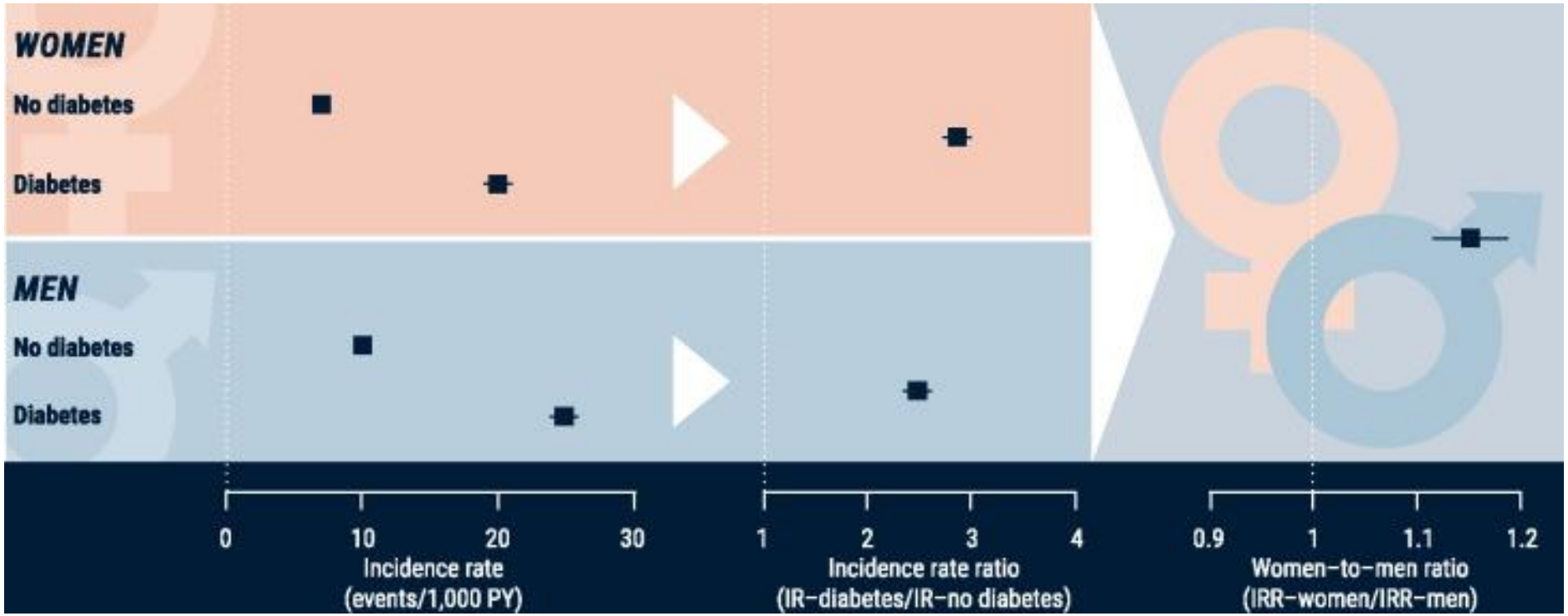


Women has major risk to develop cardiovascular diseases

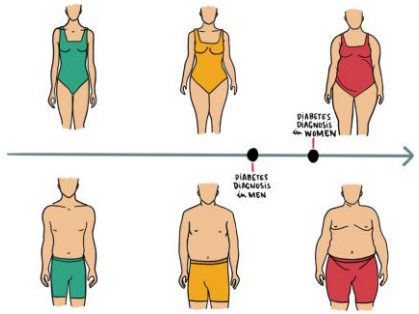
ESC European Society of Cardiology

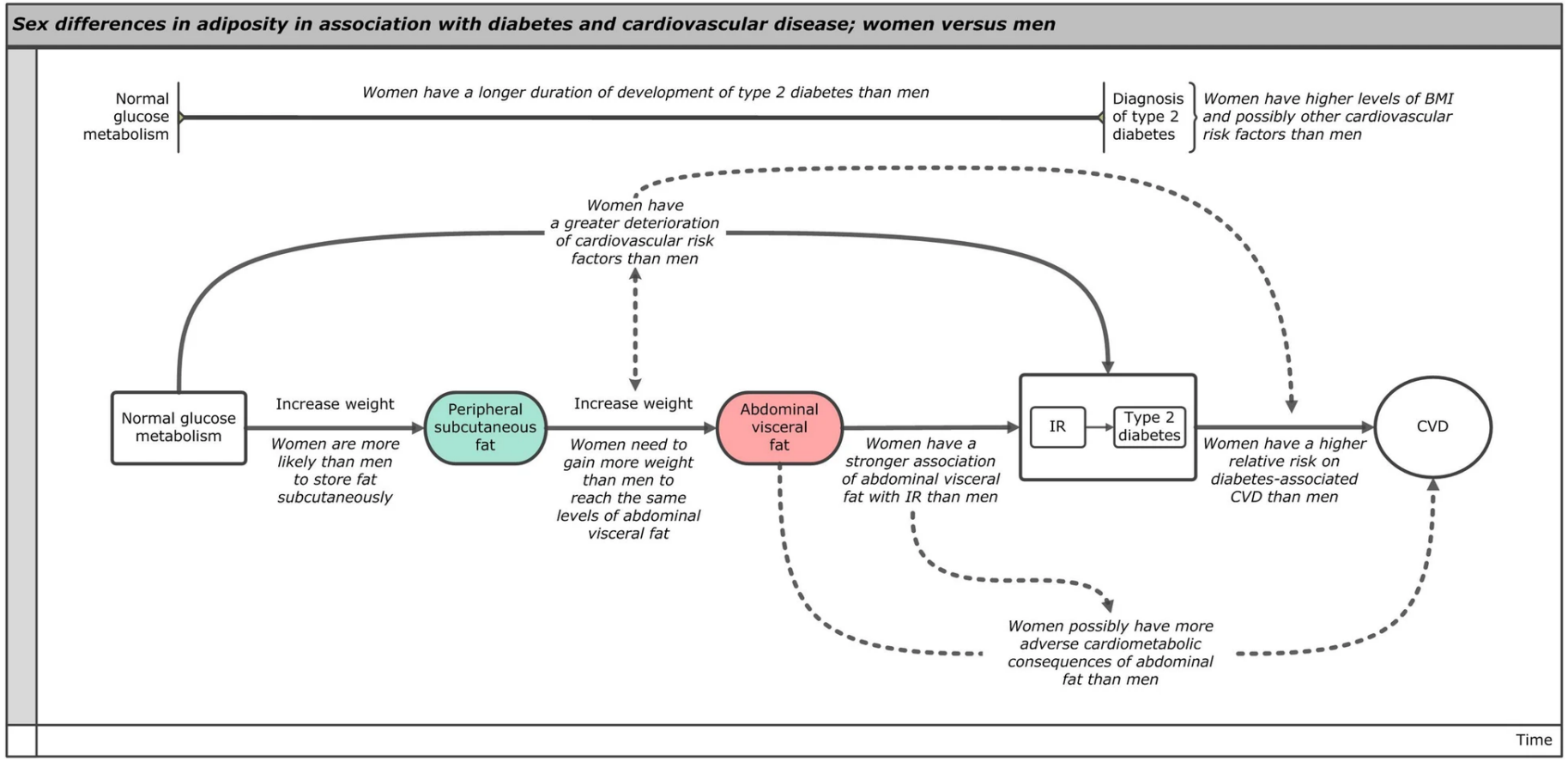


Eur Heart J. 2020 Apr 1;41(13):1346-1353. doi: 10.1093/eurheartj/ehz913.

Biology of Sex Differences

Sex differences in the risk of vascular disease associated with diabetes





Biol Sex Differ. 2020 Jan 3;11(1):1. doi: 10.1186/s13293-019-0277-z.

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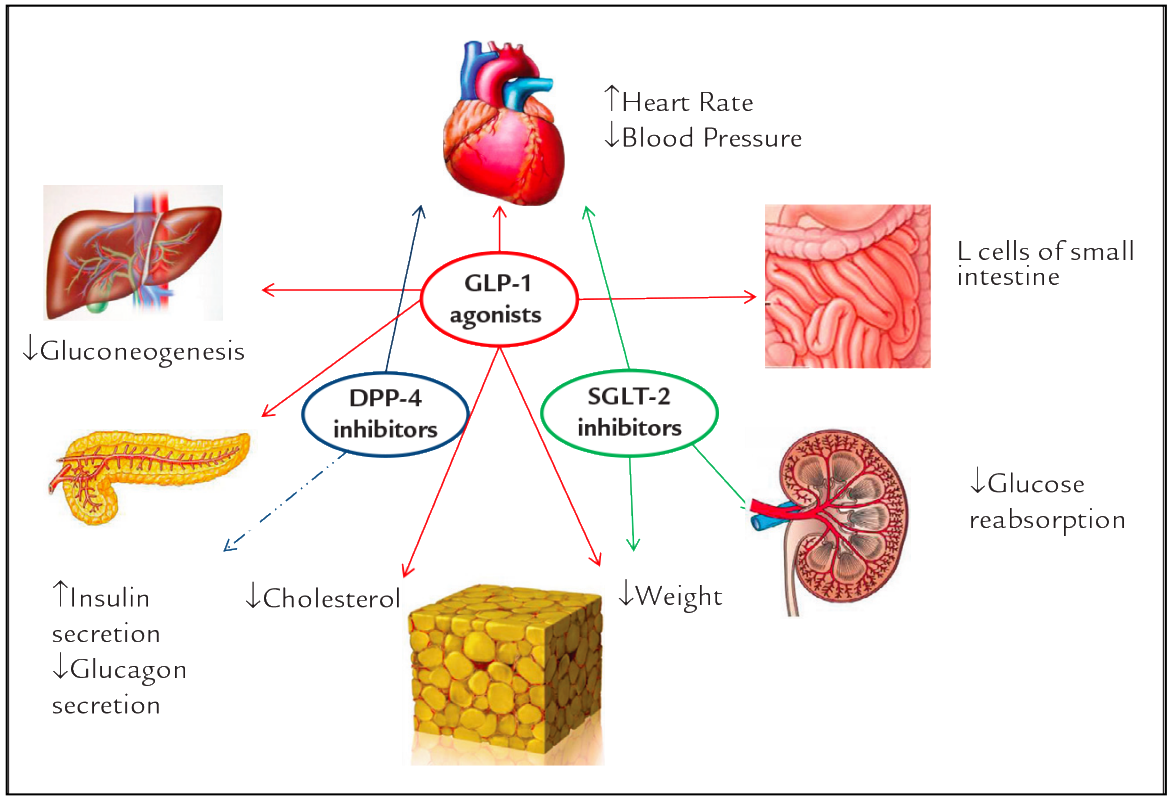


Long-Term Effectiveness of Liraglutide for Weight Management and Glycemic Control in Type 2 Diabetes

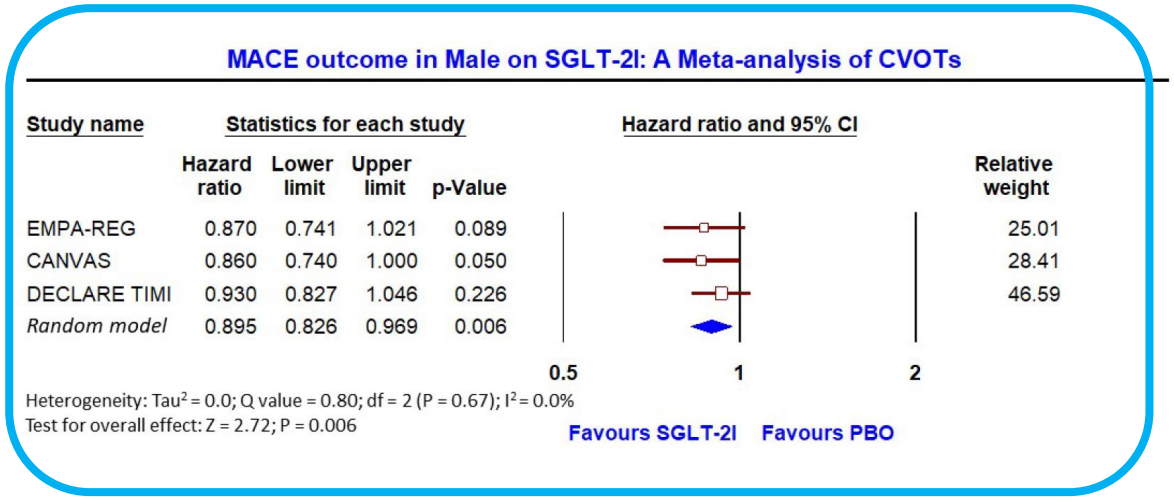
	B	Beta	T	*p*-Value
BMI	0.387	0.380	2.533	0.016
Female gender	5.086	0.365	2.420	0.020
* Female gender	6.459	0.464	2.975	0.005

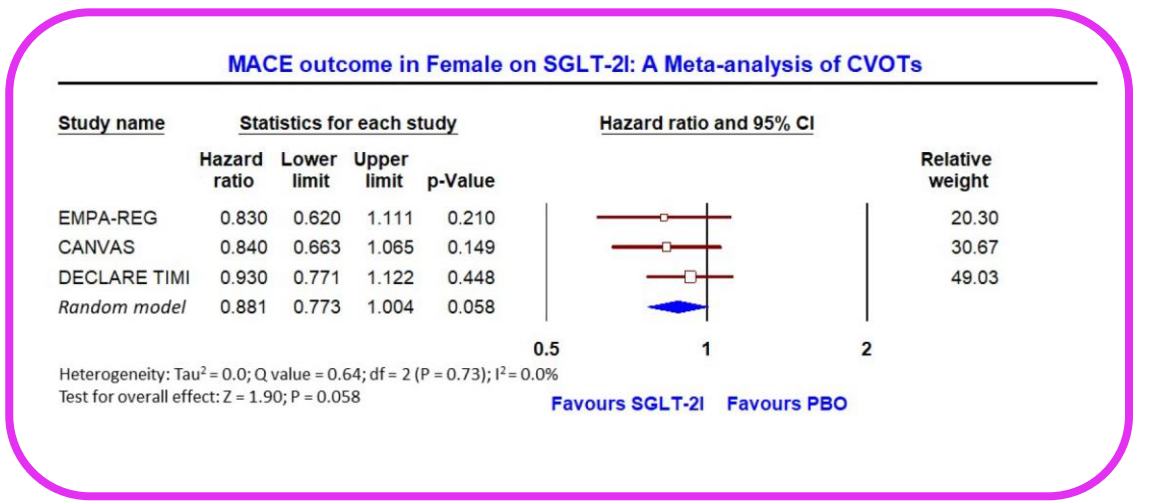
Conclusions:

Prolonging treatment with Liraglutide can lead to durable benefits in relation to weight and glycemic control, with a greater impact on women.

Int J Environ Res Public Health., Volume 17, 27 Dec 2019, doi: 10.3390/ijerph17010207.

Gender difference in Cardiovascular Outcomes with SGLT-2 inhibitors and GLP-1 receptor agonist in Type 2 Diabetes:
A Systematic Review and Meta-analysis of Cardio-Vascular Outcome Trials





Diabetes Metab Syndr. 2020 May-Jun;14(3):181-187. doi: 10.1016/j.dsx.2020.02.012.

Conclusions

- Sex is a fundamental biological factor, which plays a key role in regulation of homeostasis in health and causes vulnerability to cardiometabolic risk factors, as well as manifestation, clinical picture, and management of T2DM;

- The care of diabetic pregnancy demands special attention, because this vulnerable phase programs health of offspring even in a sex-specific way;

- Psychosocial factors also impact development and progression of diabetes and coping in a gender-dimorphic way.

Modern personalized treatment has to consider differences in biological factors, like genetic predisposition, sex hormones, and neurohumoral pathways, as well as behavioral and environmental differences between men and women