סוכרת: למה "מתוקה" סובלת יותר?

ד"ר יואל טולדנו

מומחה ברפואה פנימית ובאנדוקרינולוגיה

יחידת אם ועובר, בי"ח לנשים ע"ש הלן שניידר, מרכז רפואי רבין

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- Introduction
- Evidence of sex-differences in diabetes-associated CVD risk
- Potential Explanations for the excess CV risk in women with diabetes
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מקרה- ״מתוקה״

- בת 56, אם ל-3 , עקרת בית
- פנתה לבקורת לאחר אשפוז עם MI
- סוכרת מסוג 2- לא מאוזנת, היפוגליקמיות
- HbA1c 8.6%
- גלוקוז בצום 170 ,פוסטפרנדיאל עד 250

- רקע רפואי:
- Gestational DM, שטופלה בדיאטה, במהלך היריון אחרון בגיל 40
- לאחר לידה- נורמוגליקמיה
- בגיל 48 שנה אובחנה סוכרת מסוג 2
- מנופאוזה מגיל 50

- תזונה- מתקשה לשמור
- פעילות גופנית- מועטה ולא סדירה
- תרופות- Metformin 850 mg*3/d , Amaryl 4 mg*1/d

מקרה- ״מתוקה״

איברי מטרה של סוכרת:

- עיניים- בדיקת פונדוסים לפני 3 חודשים תקינה.
- כליות- דגימת שתן ליחס Microalbumin/Creatinine תקינה לפני חודש
- ללא נוירופטייה.
- Cardiovascular / Macrovascular- IHD, לאחר MI

גורמי סיכון קרדיו-וסקולריים:

- שוללת עישון
- BMI 27 משקל 70 ק״ג, גובה 160 ס״מ
- ל״ד 130/80
- דיסליפידמיה- LDL 125 TG 178 HDL 44

מקרה- ״מתוקה״

- בת 56, אם ל-3 , עקרת בית
- פנתה לבקורת לאחר אשפוז עם MI
- סוכרת מסוג 2- לא מאוזנת, היפוגליקמיות, HbA1c 8.6%, גלוקוז בצום 170 ,פוסטפרנדיאל עד 250

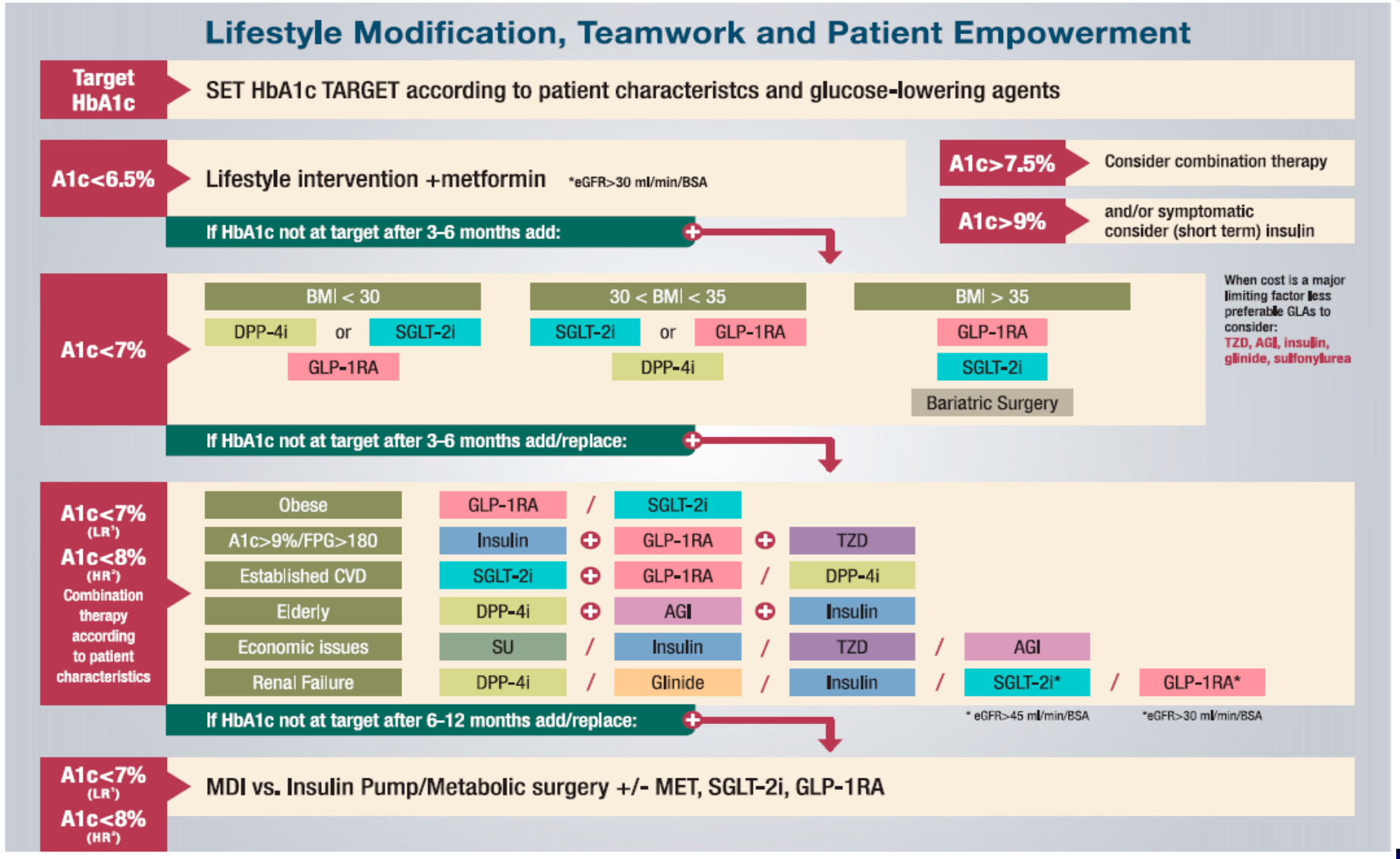
- רקע רפואי:
- בגיל 48 שנה אובחנה סוכרת מסוג 2, מצב לאחר GDM, מנופאוזה מגיל 50

- תזונה- מתקשה לשמור דיאטה; פעילות גופנית- מועטה ולא סדירה
- תרופות- Metformin 850 mg*3/d , Amaryl 4 mg*1/d

- פגיעה באיברי מטרה- IHD, לאחר MI
- עודף משקל ודיסליפידמיה

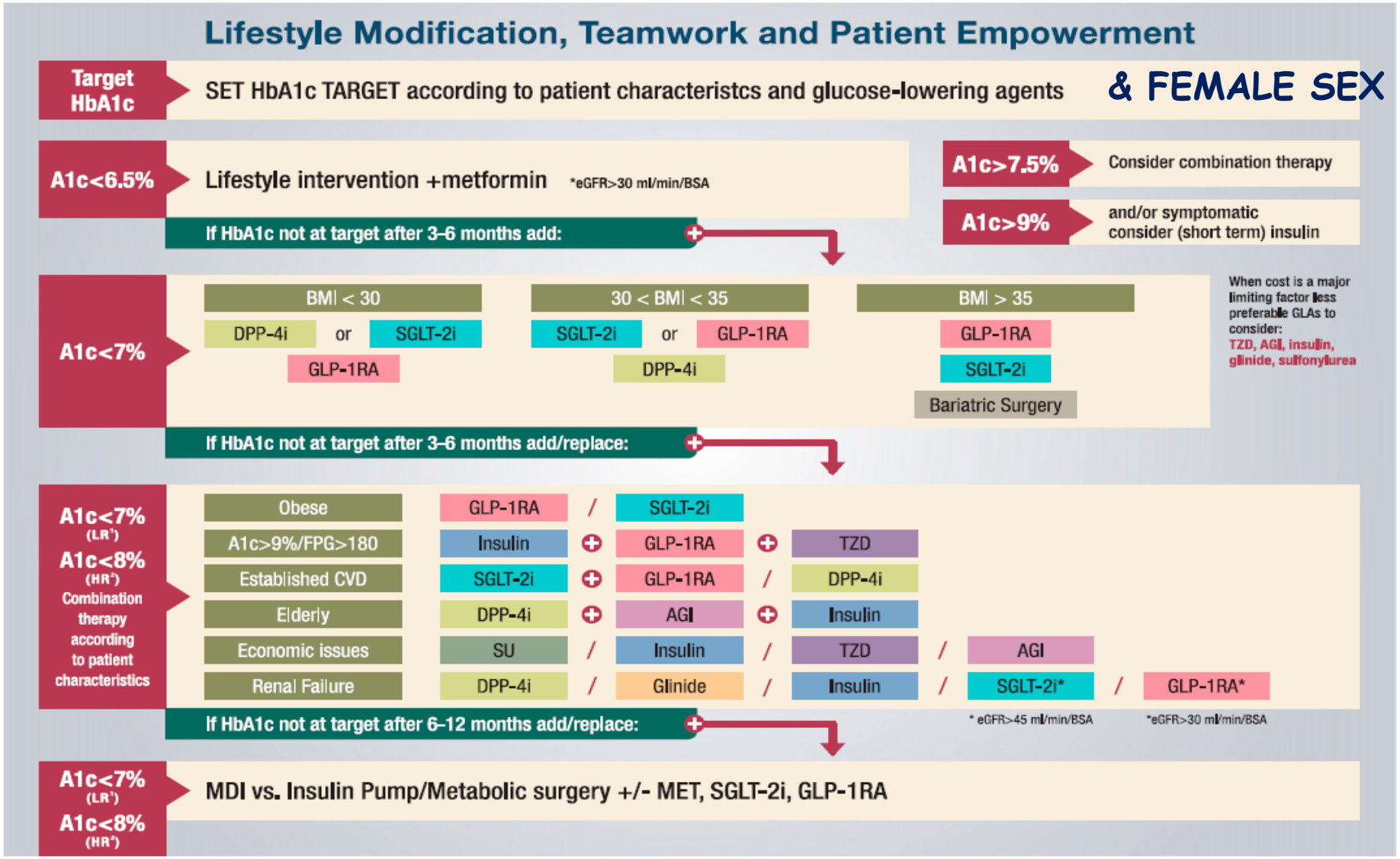
מה השלב הבא באלגוריתם הטיפולי בסוכרת?

הנחיות המועצה הלאומית לסוכרת 2016



Mosenzon O, Pollack R, Raz I; Diabetes Care 2016

הנחיות המועצה הלאומית לסוכרת 2016: בואו נציע גם להתחשב ב- SEX



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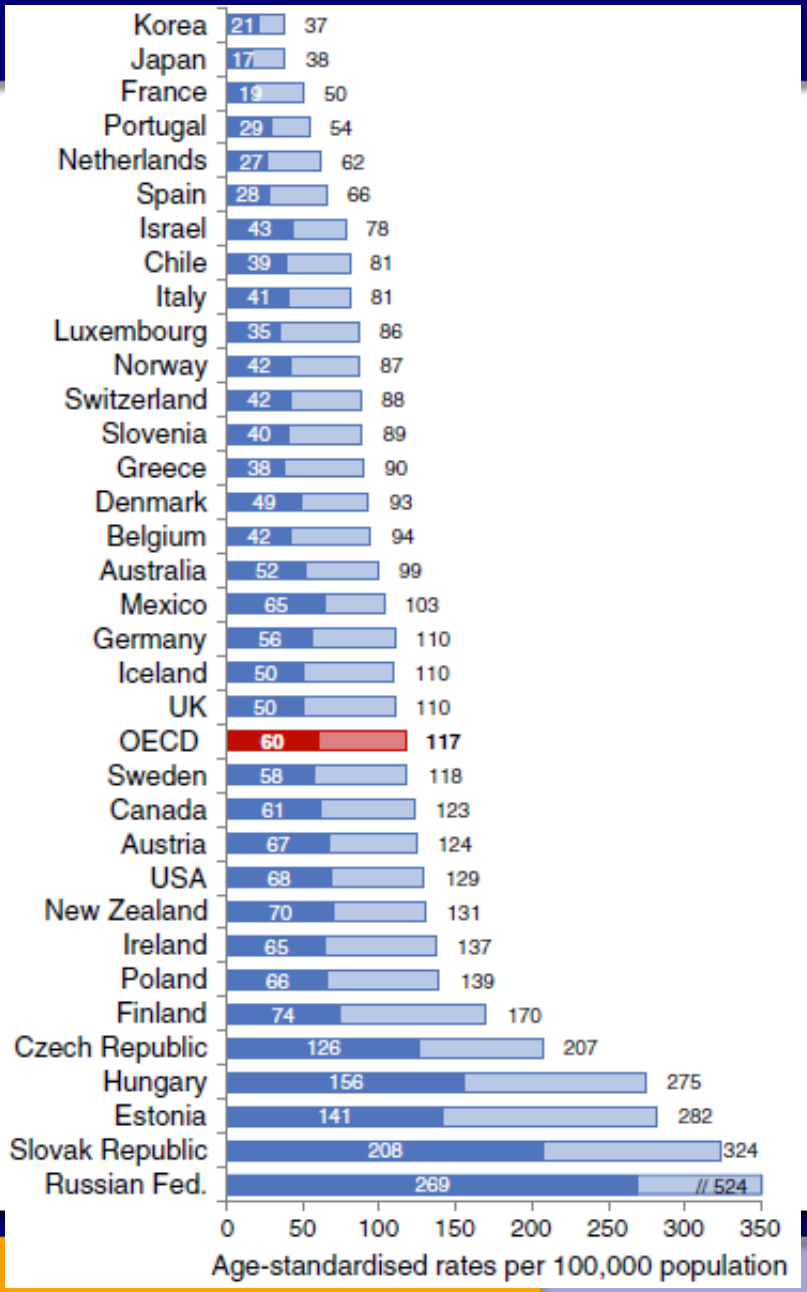
Excess CV Risk in Diabetes

- Diabetes is associated with increased CV risk
- ~50% of diabetics will die of a CV cause
- Diabetes may confer an equivalent risk to aging 15 years
- Diabetes prevalence is increasing
- There is no clear evidence that diabetes prevalence differs between men and women

Mortality rates for IHD in men and women, 2009



Women-Dark blue

Men- Light blue

Norhammar A, Diabetologia 2013

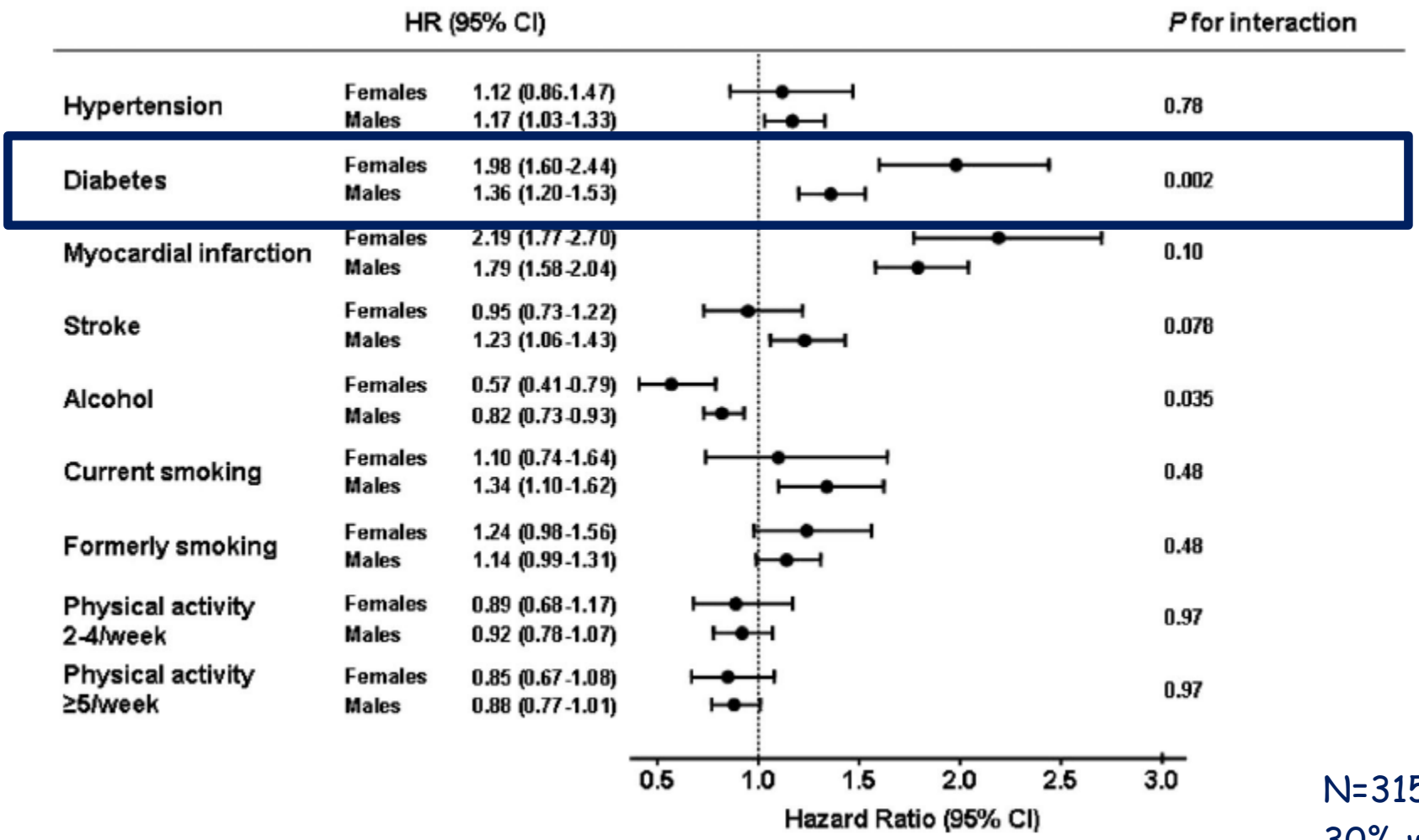
The sex gap: Excess CV risk in women

- Diabetes increases CVD risk and mortality by two to four times
- However, diabetes has a different impact in women and men
- It increases the risk by about four times in women and about twofold in men

The sex gap: Age gap of CVD in women vs. men

- CVD presents about 10 years later in women than in men
- But this age gap is almost completely attenuated when diabetes is present
- It is therefore possible to conclude that women with diabetes lose their normal 'female' protection from CVD.
- One consequence is that women with diabetes suffer myocardial infarctions several years earlier than women without diabetes, approaching the same age of onset for myocardial infarction as men

Sex differences in risk factor and clinical associations with acute MI



N=31546
30% women
37% with DM

Kappert K, Circulation 2012

Diabetes increases fatal coronary heart disease in women

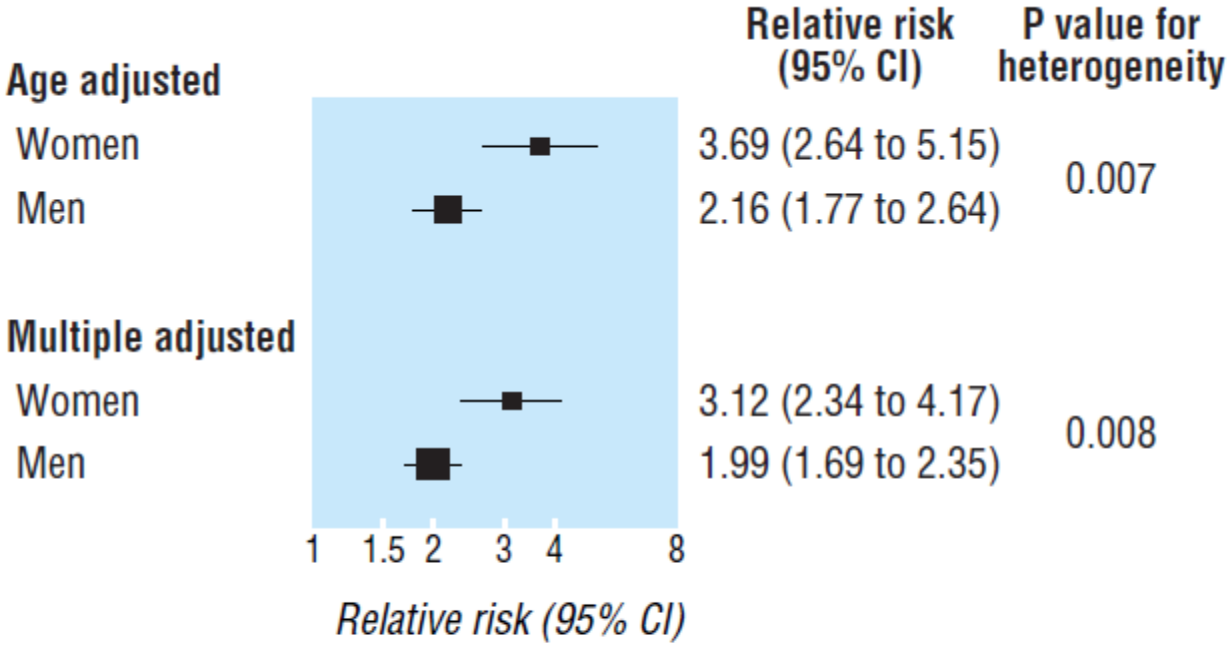
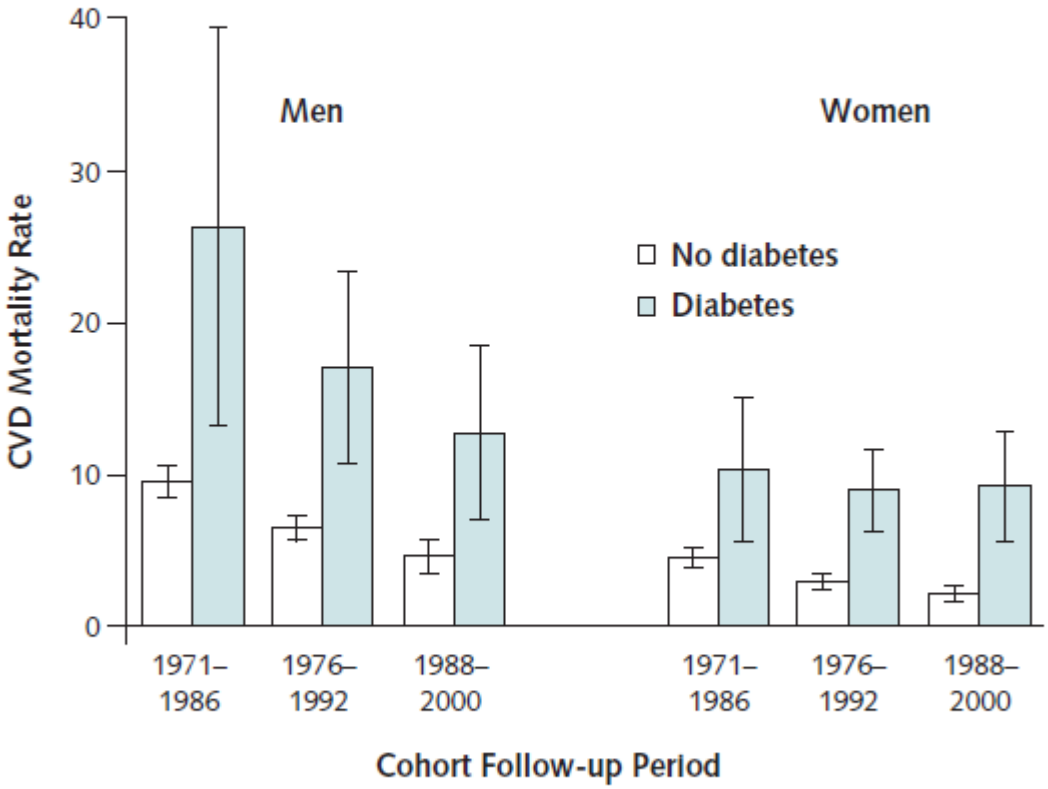


Fig 2 Overall summary estimates of relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes in 22 studies that reported both age and multiple adjusted coefficients

Huxley R, BMJ 2006

The decline in CVD deaths in the western world has not been observed to the same extent in in women with diabetes

Figure 2. Age-adjusted cardiovascular disease mortality rates among the U.S. population age 35 to 74 years with and without diabetes, by cohort and sex.



Mortality rates are calculated as annual deaths per 1000 persons. Error bars represent 95% CIs.

Gregg EW, Ann Intern Med 2007

Mortality Gap: Mortality after MI in patients with diabetes in Sweden in 1995-2002 by sex

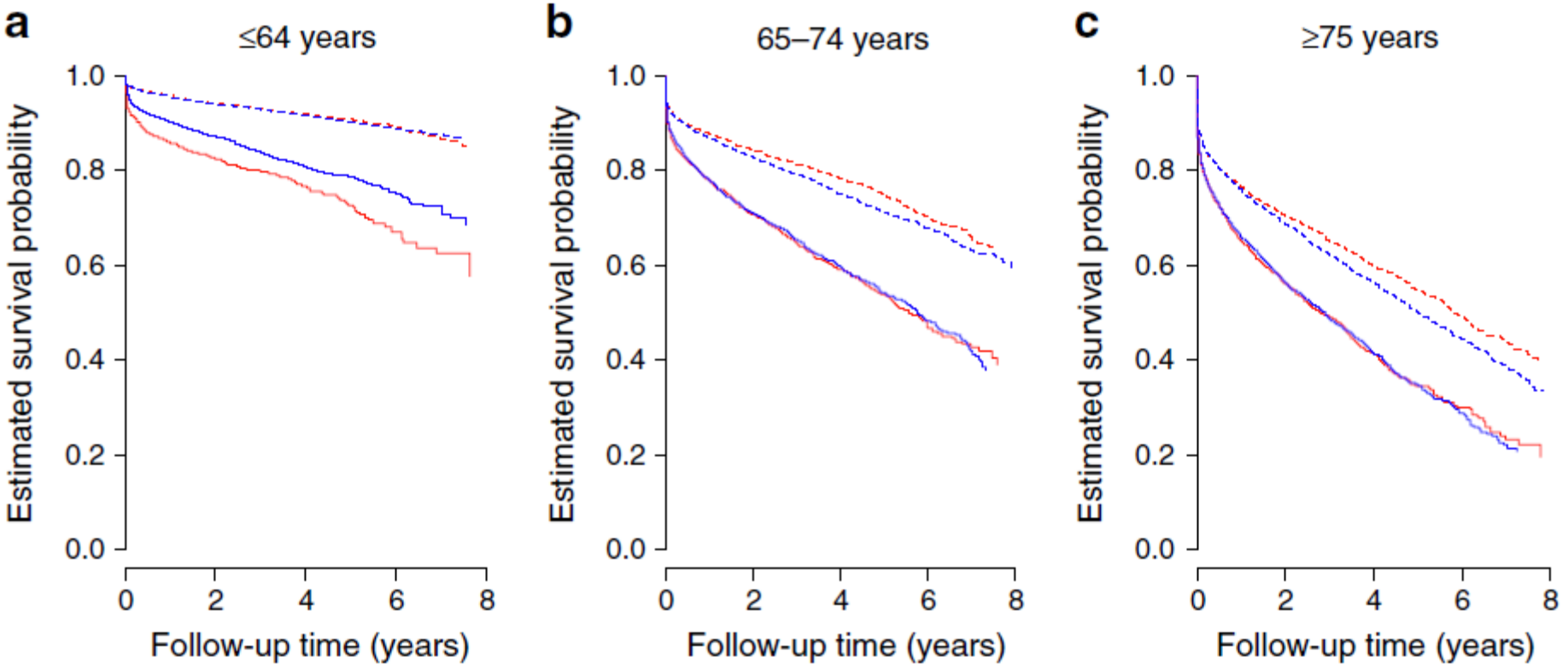
- Diabetes is an independent predictor of adverse outcome

- The mortality gap after a coronary event between patients with and without diabetes increases with follow-up time, even after modern treatment techniques

- At age under 65 years, women with diabetes had the poorest outcome after a coronary event, even worse than men with diabetes

Norhammar A, Heart 2008

Mortality Gap: Mortality after MI in patients with diabetes in Sweden in 1995-2002 by sex



Red broken line, non-diabetic women;
Red solid line, women with diabetes;
Blue broken line, non-diabetic men;
Blue solid line, men with diabetes

N=70,882
31% women
21% with diabetes mellitus

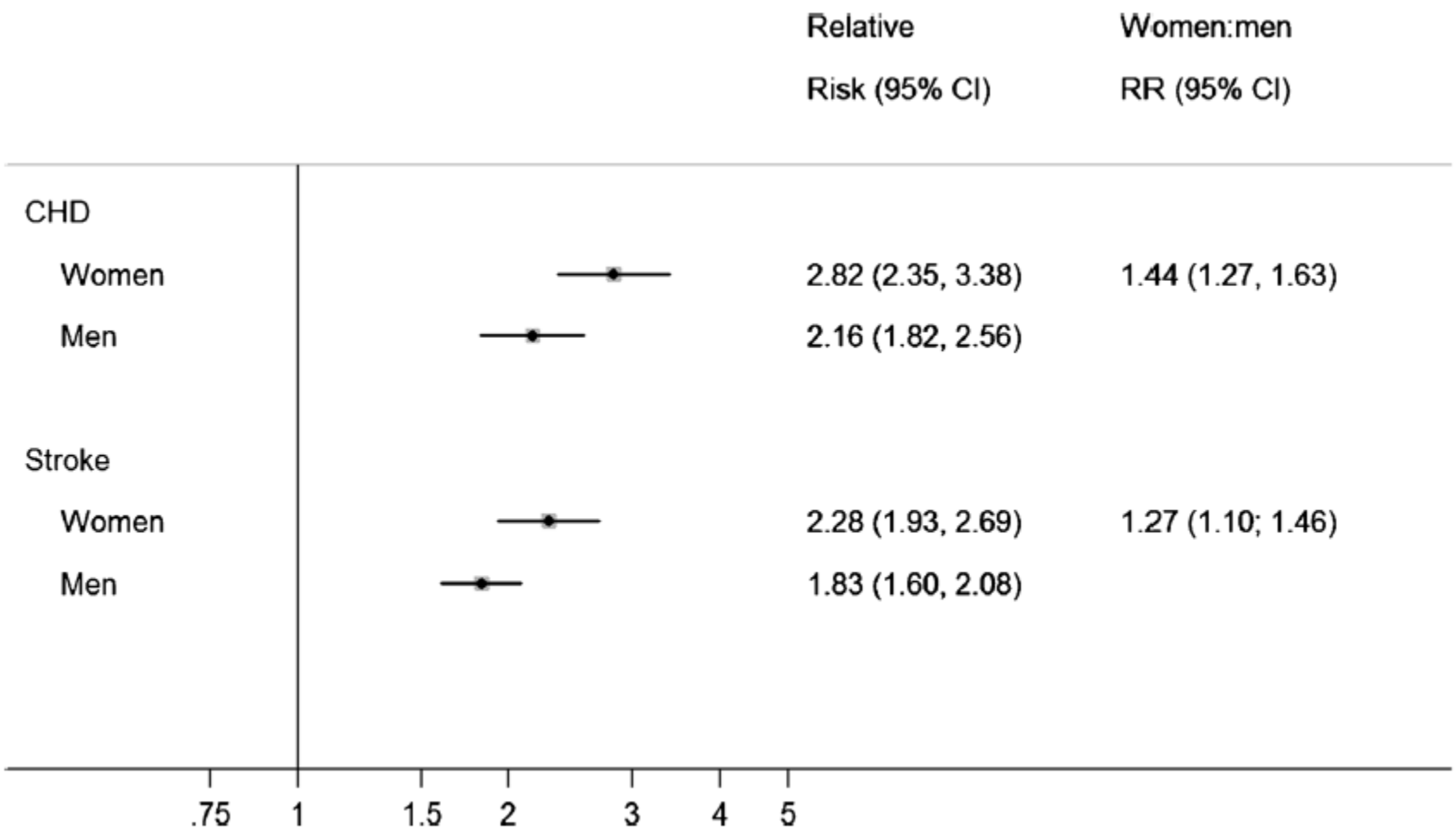
Norhammar A, Heart 2008

Gender difference in diabetes

Does the difference between genders is the same for each CV event?

i.e. CHD, stroke, CHF, lower extremity amputation etc.

Increased relative risk and women:men ratio of RR for CHD and stroke in women and men with vs. without diabetes



Peters et al, Curr Cardiovasc Risk Rep 2015

Taking together……

- Female sex has a protective effect on cardiovascular risk
- Diabetes greatly attenuates, or may even reverse, this protective effect
- This gender difference has obvious implications in the attempt to optimize preventive and therapeutic interventions

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Reasons for the "sex gap": Related disorders

- In women, risk factors considered to be related to early CVD in the absence of known diabetes:

✓ Polycystic ovary syndrome
✓ Premature menopause
✓ Gestational diabetes
✓ Hypertension
✓ A history of pre-eclampsia
✓ Lactation! has emerged as a factor related to CVD: a longer lactation period appears to have a protective effect when it comes to future CVD [Stuebe AM, Gynecol 2009]

An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Michael Sherf,[3] Eyal Sheiner[1]

- **Soroka University Medical Center**
- ***A cohort of women with/without a diagnosis of GDM***
- **Delivered during the years 1988-1999**
- ***A follow-up period until 2010***

Table 1 Characteristics of patients during the follow-up period divided into those with and without a history of gestational diabetes mellitus (GDM)

Characteristic	GDM (n=4928)	No GDM (n=42 981)	p Value
Maternal age at index birth (years), mean±SD	32.4±6	29.4±6	0.001
Ethnicity (%)			
Jewish	67.7	72.6	0.001
Bedouin	32.3	27.4	
Total hospitalisation duration (days), mean±SD	10.6±18.3	10.3±19.7	0.740

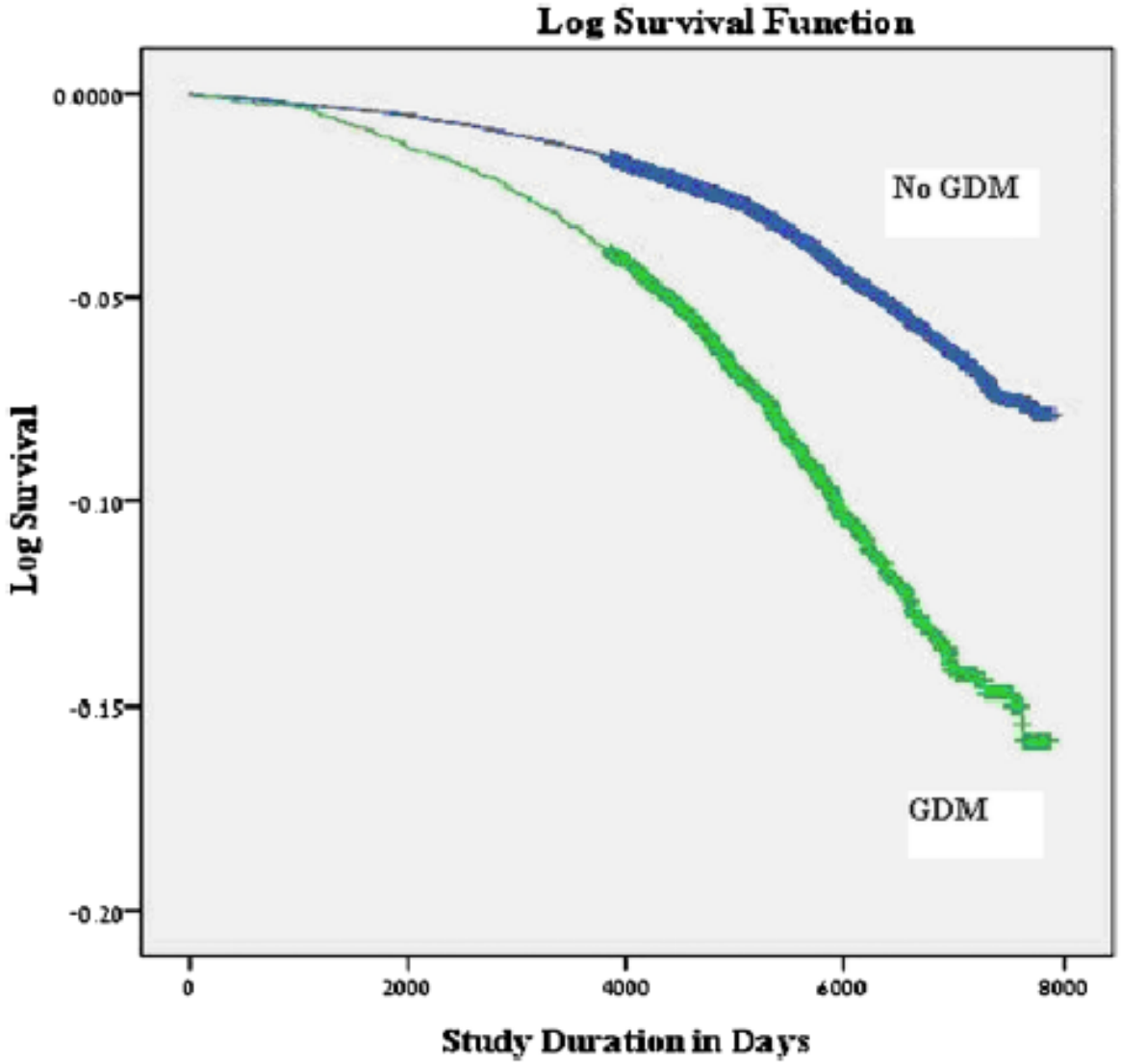


Figure 1 Kaplan–Meier survival analysis curve (presenting the log survival function) for cardiovascular-associated hospitalisation of patients with and without a history of gestational diabetes mellitus (GDM). p=0.001 (log rank test). This figure is only reproduced in colour in the online version.

GDM is an independent risk factor for long-term CV morbidity

Table 3 Cox multivariate regression model for the risk of cardiovascular hospitalisation

	Adjusted HR	95% CI	p Value
Gestational diabetes mellitus	2.6	2.3 to 2.9	0.001
Obesity (pre-gestational BMI >30 kg/m^2)	2.5	1.9 to 3.2	0.001
Pre-eclampsia	2.4	2.1 to 2.8	0.001

BMI, body mass index.

GDM is an independent risk factor for long-term CV morbidity

- Women with gestational diabetes run a particularly high risk of future CVD

- A substantial part of this risk is attributed to the subsequent development of type 2 diabetes
- Highlighting the importance of diabetes prevention in this group

- Consequently, the prevention of weight gain and abdominal obesity after pregnancy appears to be very important as, particularly in younger women, these risk factors are related to future CVD

Maternal Medicine Meets Fetal Medicine

The Vicious Cycle - NCD Epidemic

Obesity ,Diabetes, Metabolic Syndrome & Pregnancy

Pedersen & Freinkel Hypothesis

Diagnosis & Management

Abnormal Intrauterine Metabolic environment

Programming & Imprinting

Childhood Obesity

Early Metabolic syndrome

PCOS

Adult Obesity

Early T2DM

Pre-Pregnancy Management

Pregnancy complicated with Diabesity (Obesity /GDM/PGDM)

Reasons for the "sex gap": Clustering

Table 2 Clinical characteristics and major cardiovascular disease risk factors in men and women by age.

Variables	Age < 65		p	Age ≥ 65		p
	Women (n = 800)	Men (n = 944)		Women (n = 368)	Men (n = 353)	
Age (years)	58 ± 4	58 ± 4	0.189	67 ± 2	67 ± 2	0.612
Diabetes duration (years)	7 (7)	7 (7)	0.703	10 (11)	9 (11)	0.788
Waist circumference (cm)	101 ± 13	101 ± 11	0.565	100 ± 13	101 ± 10	0.350
BMI (Kg/m^2)	**31.1 ± 5.7**	**28.8 ± 4.0**	**0.001**	29.8 ± 5.7	28.2 ± 4.1	0.001
Systolic blood pressure (mmHg)	**141 ± 17**	**139 ± 15**	**0.014**	146 ± 17	145 ± 16	0.310
Diastolic blood pressure (mmHg)	84 ± 9	85 ± 9	0.050	84 ± 8	84 ± 9	0.426
Heart rate (beat/min)	75 ± 10	72 ± 10	0.001	74 ± 12	72 ± 11	0.007
Fasting plasma glucose (mg/dL)	**159 ± 47**	**153 ± 42**	**0.002**	161 ± 48	157 ± 43	0.176
Glycated haemoglobin (%)	**7.7 ± 1.5**	**7.5 ± 1.4**	**0.001**	7.7 ± 1.3	7.5 ± 1.2	0.038
HDL cholesterol (mg/dL)	52 ± 13	45 ± 11	0.001	54 ± 13	48 ± 12	0.001
Triglycerides (mg/dL)	139 (91)	131 (33)	0.066	138 (98)	132 (90)	0.663
LDL cholesterol (mg/dL)	**135 ± 34**	**131 ± 33**	**0.014**	136 ± 33	128 ± 36	0.001
Non-HDL cholesterol (mg/dL)	166 ± 38	163 ± 37	0.092	167 ± 36	157 ± 37	0.001
Fibrinogen (mg/dL)	338 ± 83	319 ± 74	0.001	354 ± 87	331 ± 81	0.001
Current smokers (%)	142 (17.8%)	287 (30.4%)	0.001	55 (15.0%)	68 (19.3%)	0.138

Data are given as mean ± SD or median and (interquartile range) or as number and (%).
Significant values ($p < 0.05$) are highlighted in bold.

Cross-sectional survey T2DM: 1297 men, 1168 women; No CVD

Franzini L, Nutr Metab Cardi Dis 2013

Reasons for the "sex gap": Clustering

- The impact of existing and clustering risk factors in women vs. men

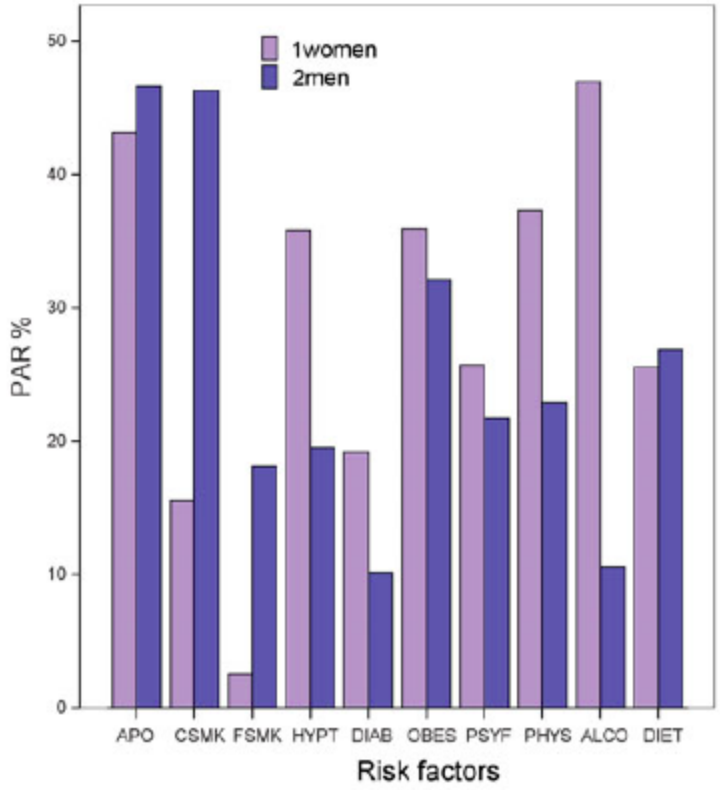
- The sex difference for age at first myocardial infarction in the general population-

  d/t higher levels of risk factors at younger ages in men compared with women?

  such as blood lipids, smoking and family history

Comparison of risks between women and men

Risk factor		Odds ratio (95% CI)	PAR (95% CI)	*P* interaction
ApoB/ApoA1 ratio	♀	3.30 (2.85,3.82)	43.1 (38.2,48.1)	0.20
	♂	2.87 (2.63,3.13)	46.6 (43.3,50.0)	
Current smoking	♀	2.86 (2.47,3.32)	15.5 (13.5,17.5)	0.06
	♂	3.04 (2.84,3.26)	46.3 (44.1,48.4)	
Former smoking	♀	1.04 (0.88,1.22)	2.5 (0.6,4.5)	<0.0001
	♂	1.61 (1.49,1.74)	18.1 (15.2,21.1)	
Hypertension	♀	2.95 (2.66,3.28)	35.8 (33.0,38.6)	0.0001
	♂	2.32 (2.16,2.48)	19.5 (18.1,21.0)	
Diabetes	♀	4.26 (3.68,4.94)	19.1 (17.2,21.0)	<0.0001
	♂	2.67 (2.43,2.94)	10.1 (9.2,11.0)	
Abdominal obesity	♀	2.26 (1.98,2.57)	35.9 (30.3,41.5)	0.03
	♂	2.24 (2.08,2.42)	32.1 (28.8,35.4)	
Psychosocial	♀	3.49 (2.40,5.09)	25.7 (18.4,33.1)	0.02
	♂	2.58 (2.11,3.15)	21.7 (17.0,26.4)	
Physical inactivity	♀	2.07 (1.77,2.43)	37.3 (28.0,46.6)	<0.0001
	♂	1.30 (1.20,1.41)	22.9 (17.8,27.9)	
Lack of Alcohol intake	♀	2.42 (2.00,2.93)	46.9 (36.9,56.9)	<0.0001
	♂	1.13 (1.06,121)	10.5 (6.3,14.8)	
High risk diet	♀	1.78 (1.54,2.04)	25.5 (18.4,32.6)	0.20
	♂	1.68 (1.56,1.82)	26.8 (22.6,31.1)	

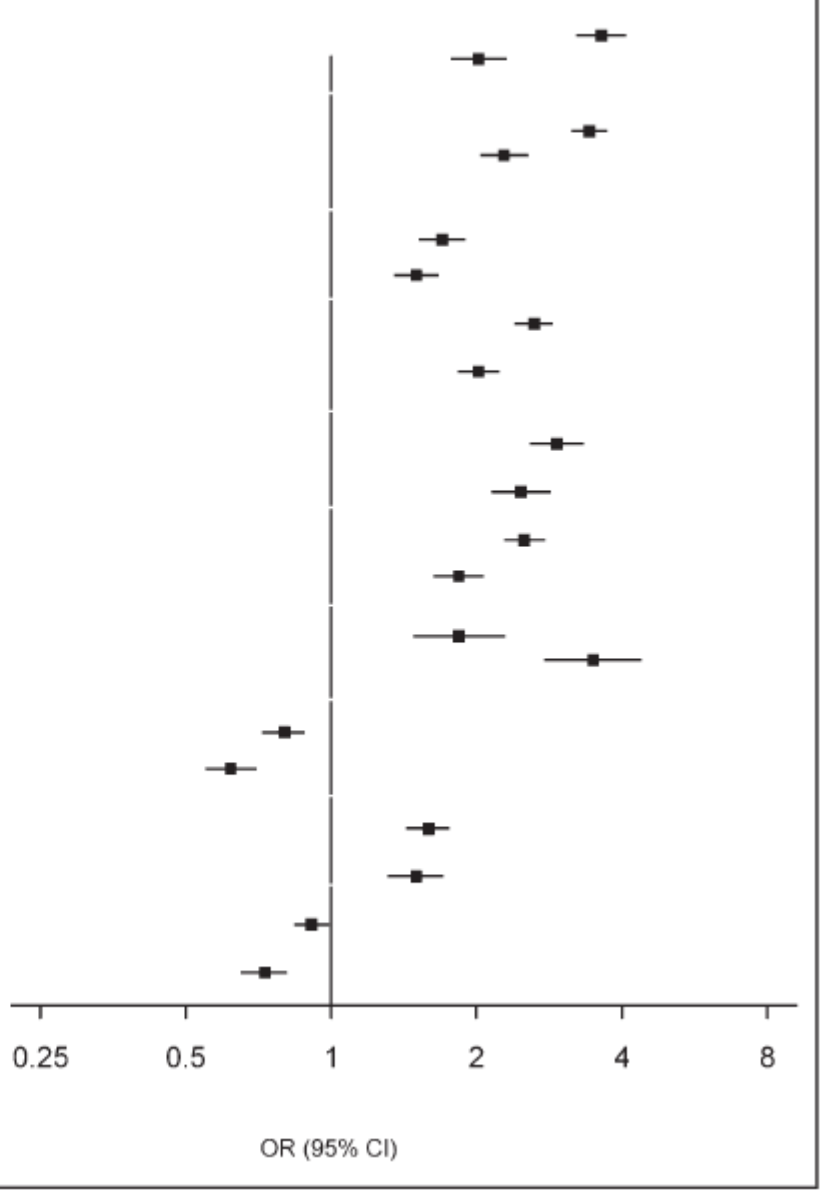


INTERHEART study
N=27098, case-control
6787 women
7.6% with DM

Anand SS, Eur Heart J 2008

Impact of risk factors in younger vs. older men

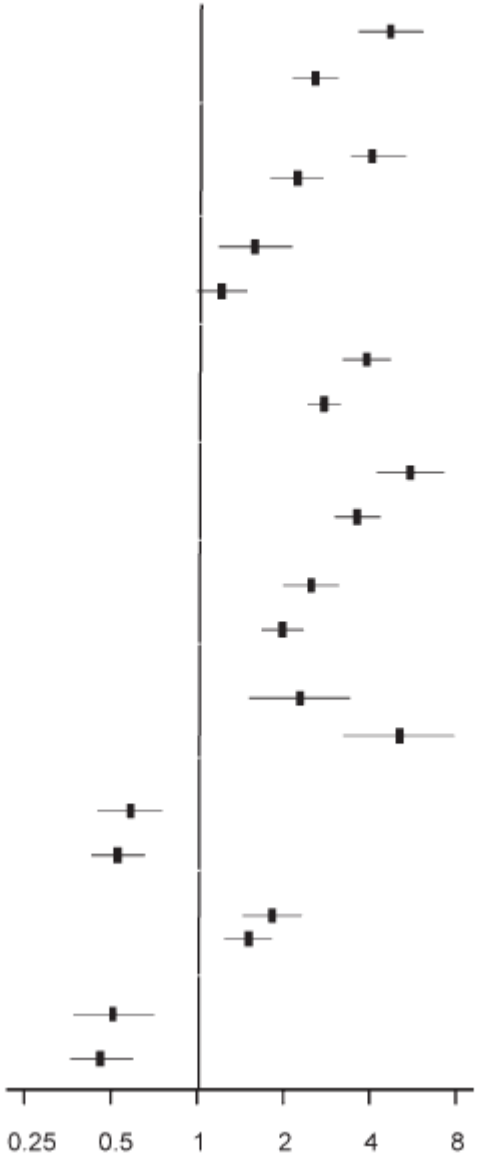
		Control prevalence	Odds ratio	*P* for Interaction
ApoB/ApoA1 Ratio	<60 years	38.31	3.63 (3.22,4.08)	<0.0001
	≥60 years	32.64	2.02 (1.77,2.31)	
Current Smoking	<60 years	39.22	3.42 (3.14,3.73)	<0.0001
	≥60 years	22.75	2.28 (2.04,2.56)	
Former Smoking	<60 years	18.96	1.70 (1.52,1.90)	0.25
	≥60 years	34.17	1.50 (1.35,1.67)	
Hypertension	<60 years	14.88	2.63 (2.40,2.88)	0.0001
	≥60 years	27.60	2.02 (1.83,2.23)	
Diabetes	<60 years	6.42	2.93 (2.58,3.33)	0.08
	≥60 years	9.00	2.47 (2.15,2.85)	
Abdominal Obesity	<60 years	31.07	2.51 (2.28,2.77)	<0.0001
	≥60 years	36.99	1.84 (1.63,2.07)	
Psychosocial	<60 years	91.13	1.84 (1.48,2.29)	0.25
	≥60 years	81.25	3.49 (2.76,4.40)	
Physical Activity	<60 years	18.86	0.80 (0.72,0.88)	0.001
	≥60 years	22.58	0.62 (0.55,0.70)	
High risk diet	<60 years	24.77	1.59 (1.43,1.76)	0.88
	≥60 years	20.90	1.50 (1.31,1.71)	
Alcohol Consumption	<60 years	29.86	0.91 (0.84,0.99)	0.0008
	≥60 years	27.79	0.73 (0.65,0.81)	



Anand SS, Eur Heart J 2008

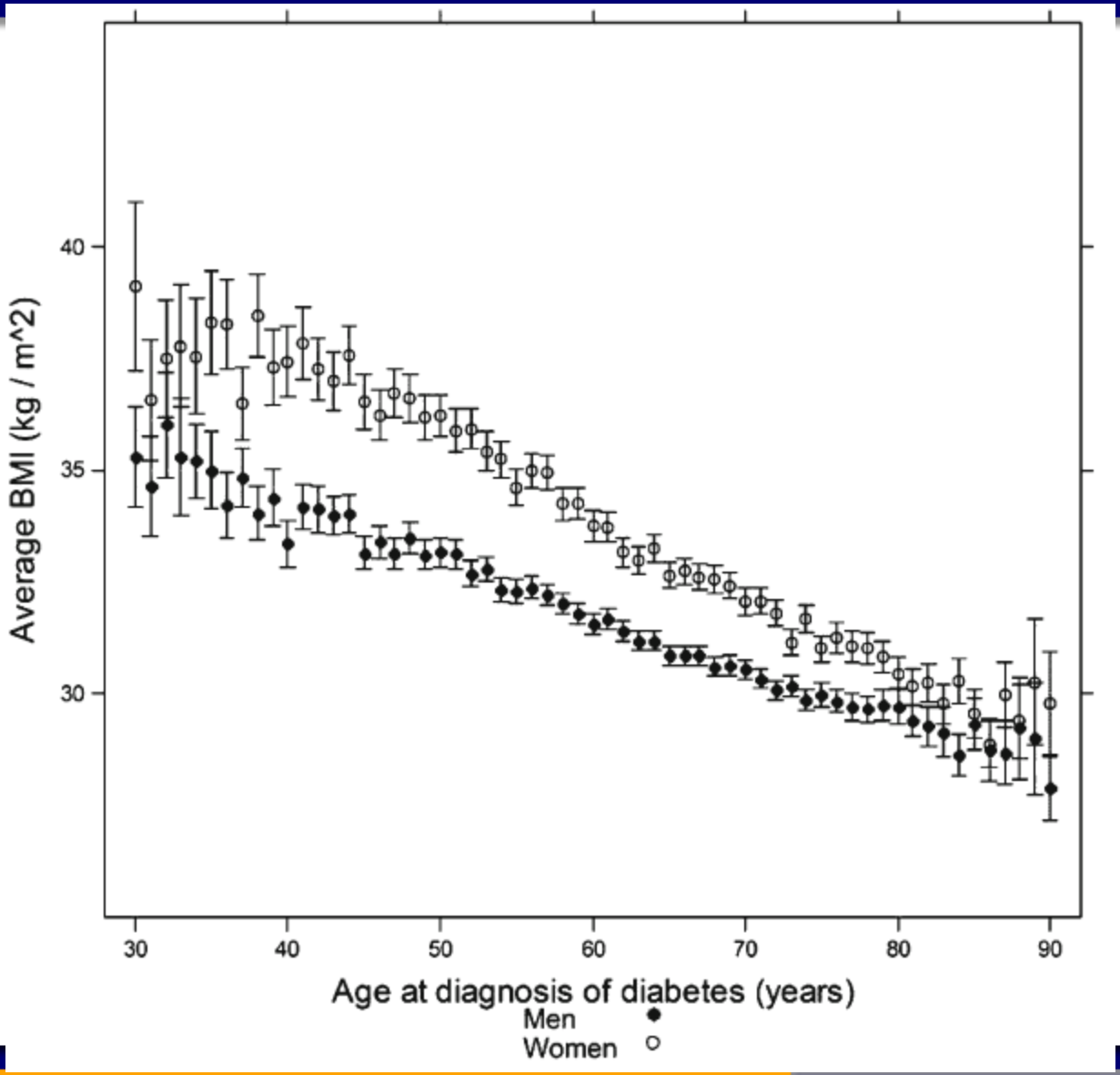
Impact of risk factors in younger vs. older women

		Control prevalence	Odds ratio	*P* Interaction
ApoB/ApoA1 Ratio[1]	<60 years	22.62	4.85 (3.76,6.28)	0.0005
	≥60 years	25.37	2.65 (2.21,3.18)	
Current smoking	<60 years	12.83	4.40 (3.54,5.48)	0.0006
	≥60 years	6.91	2.29 (1.85,2.82)	
Former smoking	<60 years	11.14	1.40 (1.05,1.88)	0.43
	≥60 years	11.89	1.17 (0.96,1.43)	
Hypertension	<60 years	19.01	4.00 (3.31, 4.84)	0.003
	≥60 years	34.44	2.84 (2.49,3.23)	
Diabetes	<60 years	6.16	5.69 (4.36,7.42)	0.008
	≥60 years	9.06	3.71 (3.10,4.45)	
Abdominal obesity [2]	<60 years	30.84	2.56 (2.05,3.19)	0.23
	≥60 years	34.96	2.03 (1.73,2.40)	
Psychosocial	<60 years	91.22	2.34 (1.56,3.49)	0.36
	≥60 years	83.29	5.22 (3.33,8.07)	
Physical activity	<60 years	17.93	0.60 (0.46,0.77)	0.55
	≥60 years	15.54	0.54 (0.44,0.67)	
High risk diet	<60 years	19.26	1.87 (1.48,2.36)	0.55
	≥60 years	16.96	1.55 (1.28,1.86)	
Alcohol Consumption	<60 years	10.87	0.52 (0.38,0.72)	0.60
	≥60 years	11.37	0.47 (0.37,0.61)	



Anand SS, Eur Heart J 2008

Reasons for the "sex gap":
Women gain more weight than men to develop diabetes



Peters et al, Curr Cardiovasc Risk Rep 2015

Reasons for the "sex gap": Insulin Resistance

- Differentially influenced in men and women by-
- ✓ Age
- ✓ sex hormones
- ✓ lifestyle factors

- The insulin-resistant state attenuated the otherwise more favourable risk profile seen in women without diabetes

Wannamethee PO, Diabetologia 2012

Reasons for the "sex gap": Medication adherence

TABLE 5. MEDICATION ADHERENCE AND TREATMENT ALIGNMENT WITH GUIDELINES FOR DIABETES AND CARDIOVASCULAR MEDICATIONS*

	Women		*Men*	
Clinical metric	n	%	n	%
Medication adherence (% of patients who are adherent)				
Oral diabetes medications (all classes)	1,748,039	64.6	1,643,695	67.5
Antihypertensive medications (all classes)	6,160,605	74.2	5,210,963	75.2
ACE-I or ARB9	3,740,105	76.6	3,606,578	76.8
Beta blocker	2,589,853	75.9	2,201,068	76.1
Cholesterol medications (all classes)	3,896,781	71.7	4,098,498	73.3
Statin	3,556,179	71.7	3,698,223	72.8
Antiplatelet medications (all classes)	477,295	79.2	607,310	81.3
Clopidogrel	421,942	80.1	546,741	82.0
Treatment alignment: Diabetes				
Use ACE-I or ARB for hypertension	1,530,265	81.2	1,439,440	84.9
Use ACE-I or ARB for hypertension, age < 65 years	632,766	81.7	708,408	88.1
Use ACE-I or ARB for hypertension, age ≥ 65	897,499	80.8	731,032	81.8
Use statin, age ≥ 45 years	1,697,807	63.1	1,625,758	66.7
Use statin, age 45–64	704,563	58.4	791,770	63.5
Use statin, age 65–75	531,983	68.6	520,133	71.2
Use statin, age > 75	461,261	64.0	313,855	67.3
A1C test in prior year	157,357	66.0	167,899	70.1
LDL-C test in prior year	154,742	60.9	165,382	64.7
Self-monitoring of blood glucose (patients on insulin)	479,077	30.0	438,869	35.1
Treatment alignment: Cardiovascular conditions				
Use cholesterol-lowering drug in presence of coronary artery disease	146,846	59.0	252,875	71.5
Use beta blocker after myocardial infarction	10,622	63.4	20,395	69.3
Use ACE-I or ARB in heart failure	67,664	54.2	71,006	59.7
Use beta blocker in heart failure	30,145	53.3	34,154	59.6

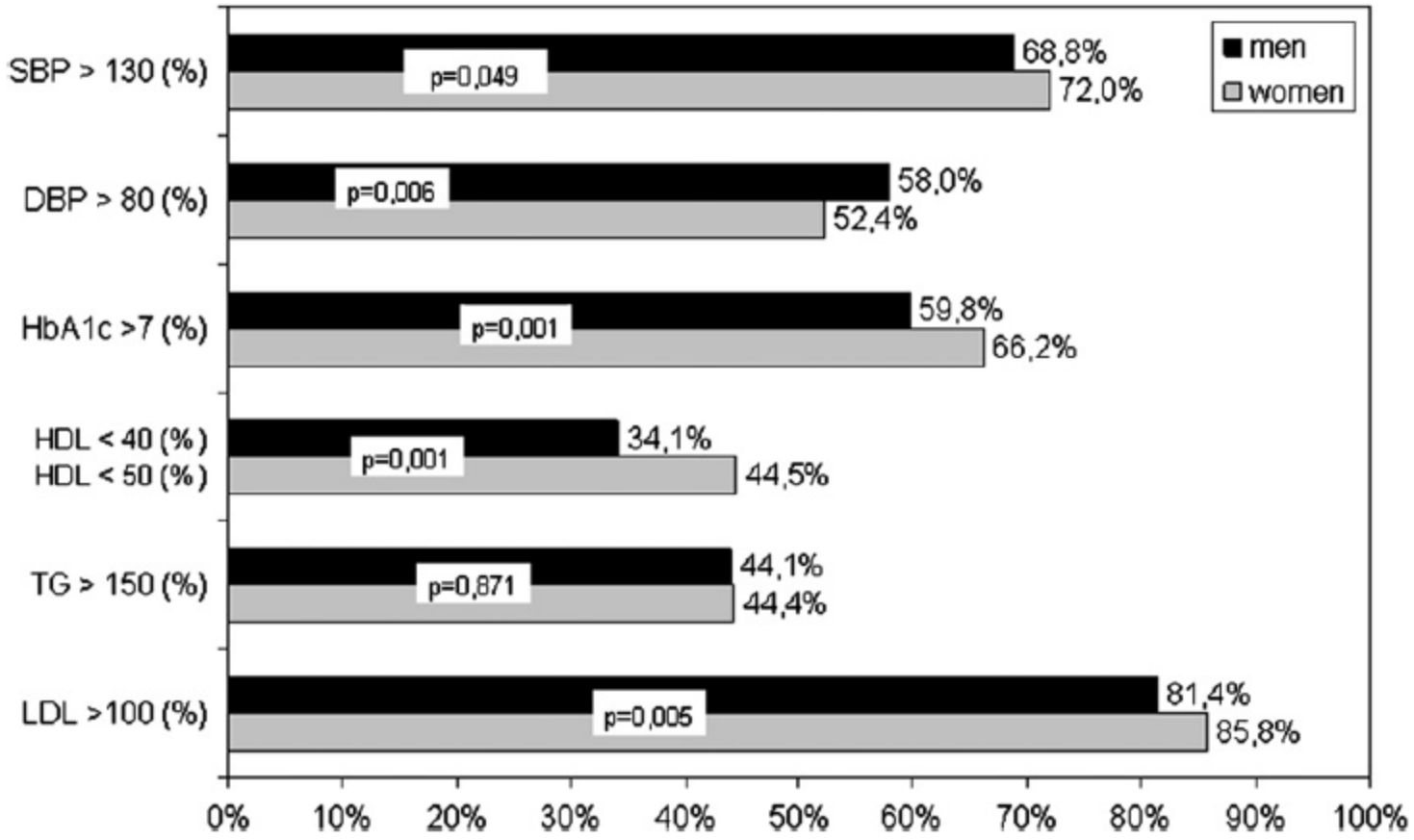
*Medication adherence is the percentage of patients who were adherent (defined as MPR ≥ 80%). Treatment alignment is the percentage of patients who received the medication or monitoring. recommended by treatment guidelines for the condition. All pairwise differences between women and men are statistically significant ($p < 0.0001$).

[redacted]ardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MPR, medication possession ratio.

29.5 million adults; 16 million women

Manteuffel M, J Womens Health 2002

Reasons for the "sex gap": Women with T2DM less likely to achieve target values



Cross-sectional survey T2DM: 1297 men, 1168 women; No CVD

Franzini L, Nutr Metab Cardi Dis 2013

Mortality Gap: Mortality after MI in patients with diabetes in Sweden in 1995-2002 by sex

- At age under 65 years, women with diabetes had the poorest outcome after a coronary event, even worse than men with diabetes

- Explanations:

✓Elevated burden of risk factors

✓Sex-related vulnerability to risk factors in younger women

✓ACE inhibitor Rx less common in women with diabetes

✓Undiagnosed heart failure-diastolic dysfunction?

✓Previous silent myocardial ischemia: Atypical ischemia d/t diabetes

✓A sex difference in the presentation of symptoms

✓The extent of atheromatosis and stenosis of the coronary arteries: Women with diabetes more frequently have significant stenosis in all three coronary arteries, to the same extent as men with diabetes, while women without diabetes more frequently have non-obstructive coronary artery disease

Norhammar A, Heart 2008

Reasons for the "sex gap": Sex Hormones?

- The role of sex hormones in this context needs to be explored more closely

סוכרת: למה "מתוקה" סובלת יותר?

- Introduction
- Evidence of sex-differences in diabetes-associated CVD risk
- Potential Explanations for the excess CV risk in women with diabetes
- **Clinical Implications and Conclusions**

Sex aspects in Cardiovascular disease

- Women's health has traditionally focused on matters related to sexual and reproductive health

- The lack of awareness of CVD in women, among both clinicians and women themselves, is especially alarming in countries with low or intermediate incomes

- There, public-health policy has largely focused on-

✓ infectious diseases, in general

✓ the maternal and reproductive health of women, in particular

Sex aspects in Cardiovascular disease

- As six in every ten deaths from CVD are related to modifiable risk factors, even among women
- Critically important: To increase the awareness of the sex aspects of CVD among healthcare providers and the general public

Summary & Recommendations

- Diabetes is a strong risk factor for future cardiovascular complications
- Diabetes attenuates the usual female advantage
- A heavy risk-factor burden in women with diabetes
- Younger women appear especially sensitive to CVD risk factors
- Sex-specific differences in risk factor management

Summary & Recommendations

- An increase in the use of primary and secondary prevention to reduce the risk-factor burden and prevent/postpone coronary events is important

- Aggressive multifactorial risk management, including lifestyle changes, has been shown to be important in reducing CV morbidity and mortality in patients with diabetes [Gaede P, NEJM 2008: Steno-2 study]

- Earlier diagnosis of CAD, before the onset of myocardial complications, is recommended

Summary & Recommendations

- History of gestational diabetes: the woman should be followed more intensively for the rest of her lifetime because of the risk of future CVD and diabetes
- Cardiologists should be encouraged to include women's health issues when taking medical histories and assessing CV risk
- More awareness of the need to include sufficient numbers of women in CV trials

Summary & Recommendations

Treat women with diabetes as aggressively as you do with their male counterparts !

מקרה- ״מתוקה״

- בת 56, אם ל-3 , עקרת בית
- פנתה לבקורת לאחר אשפוז עם MI
- סוכרת מסוג 2- לא מאוזנת, היפוגליקמיות, HbA1c 8.6%, גלוקוז בצום 170 ,פוסטפרנדיאל עד 250

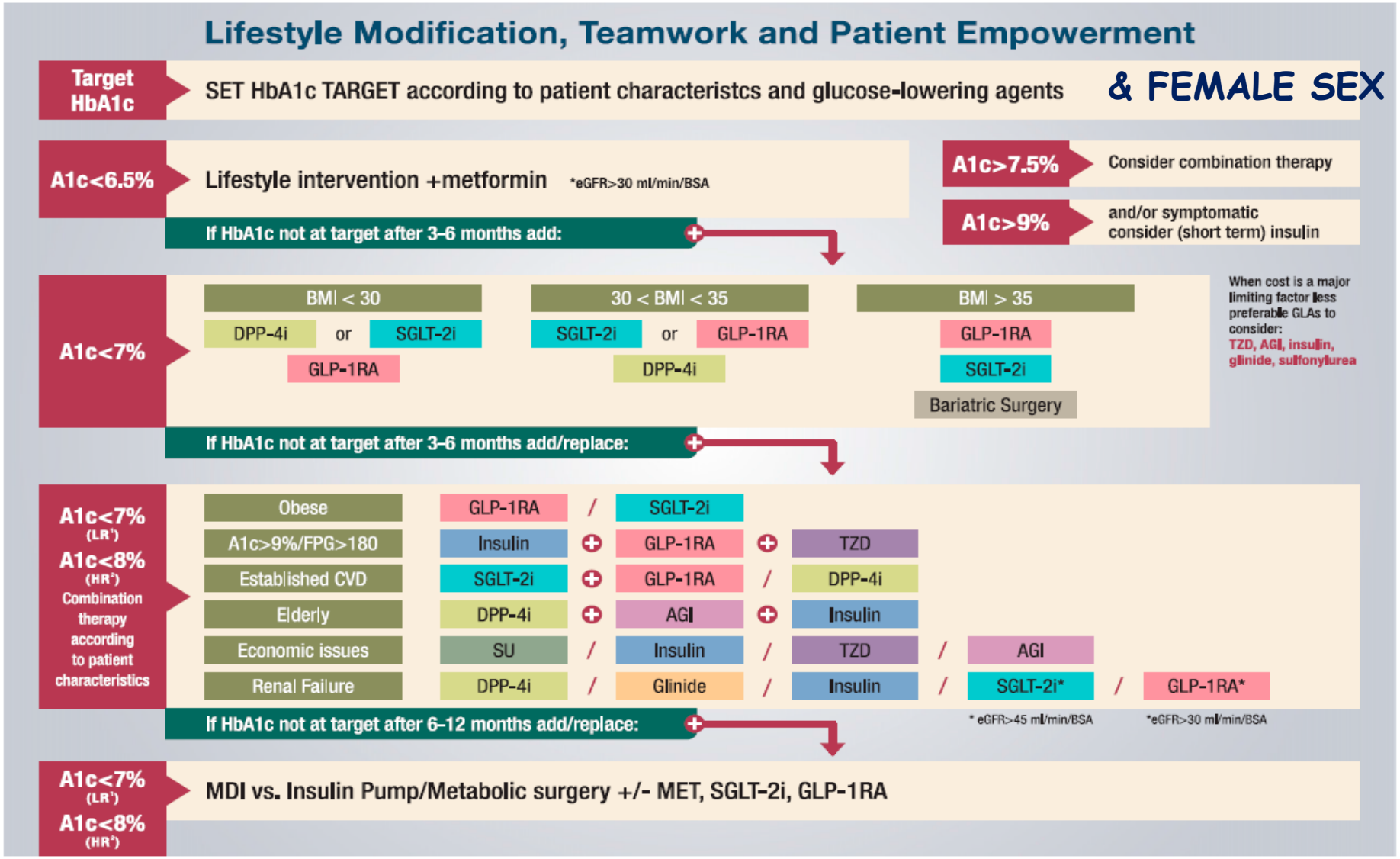
- רקע רפואי:
- בגיל 48 שנה אובחנה סוכרת מסוג 2, מצב לאחר GDM, מנופאוזה מגיל 50

- תזונה- מתקשה לשמור דיאטה; פעילות גופנית- מועטה ולא סדירה
- תרופות- Metformin 850 mg*3/d , Amaryl 4 mg*1/d

- פגיעה באיברי מטרה- IHD, לאחר MI
- עודף משקל ודיסליפידמיה

מה השלב הבא באלגוריתם הטיפולי בסוכרת?

הנחיות המועצה הלאומית לסוכרת 2016: בואו נציע גם להתחשב ב- SEX



Mosenzon O, Pollack R, Raz I; Diabetes Care 2016

הגנה CV בסוכרת מסוג 2

טיפולים פרמקולוגיים בסוכרת

משפחה פרמקולוגית	חומר פעיל	שם מסחרי	מינונים/ריכוזים זמינים	מינון מקסימלי
DPP4I	Sitagliptin	Januvia	25,50,100 mg	100 mg/day
	Linagliptin	Trajenta	5 mg	5 mg/day
	Saxagliptin	Onglyza	2.5, 5 mg	5 mg/day
	Vildagliptin	Galvus	50 mg	100 mg/day
GLP1	Exenatide	Byetta	5,10 µg	20 µg/day
	Exenatide	Bydureon	2 mg	2mg/week
	Dulaglutide	Trulicity	0.75,1.5 mg	1.5 mg/week
	Liraglutide	Victoza	6 mg/ml	1.8 mg/day
	Lixisenatide	Lyxumia	10,20 µg	20 µg/day
SGLT2I	Dapagliflozin	Forxiga	5,10 mg	10 mg/d
	Empagliflozin	Jardiance	10,25 mg	25 mg/d
SU	Glibenclamide	Gluben/Glibetic	5 mg	15 mg/d
	Glipizide	Gluco-rite	5 mg	20 mg/d
	Glimepiride	Amaryl/Glimepiride Teva	1,2,3,4 mg	8 mg/d
Meglitanides	Repaglinide	Novonorm/Repaglinide Teva	0.5,1,2 mg	16 mg/d
TZD	Pioglitazone	Actos	15,30,45 mg	45 mg/d
α Glucosidase inh.	Acarbose	Prandase/Acrose	50,100	600 mg/d
Biguanides	Metformin	Glucomin/Metformin/Glucophage	850 mg	2550 mg/d

תודה