The Diabetes Prevention Program

A Randomized Clinical Trial to Prevent Type 2 Diabetes in Persons at High Risk

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Sponsors

National Institute of Diabetes & Digestive & Kidney Diseases

Other NIH Institutes, Offices
National Center on Minority Health and Health Disparities
National Institute of Child Health and Human Development
National Institute on Aging
National Center for Research Resources, GCRC Program
Office of Research on Women's Health

Other Federal Agencies
Indian Health Service
Centers for Disease Control and Prevention

American Diabetes Association

Bristol-Myers Squibb
Warner-Lambert
LifeScan, Inc, Merck & Co., Health O Meter, Nike Sports Marketing, Hoechst Marion Roussel, Inc., Slim Fast Foods Co., Merck-Medco Managed Care, Inc, Quaker Oats Co.

DPP Primary Goal

- **To prevent or delay the development of type 2 diabetes in persons with impaired glucose tolerance (IGT)**

Study Design

- **3-group randomized clinical trial**
- **27 clinical sites**
- **Standardized across clinics:**
  - Common protocol and procedures manual
  - Staff training
  - Data quality control program

Eligibility Criteria

- **Age $\geq$ 25 years**

- **Plasma glucose**
  - **2 hour glucose 140-199 mg/dl**

    and

  - **Fasting glucose 95-125 mg/dl**

- **Body mass index $\geq$ 24 kg/m^2**

- **All ethnic groups**

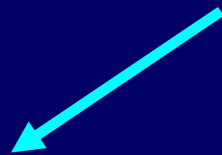 **goal of up to 50% from high risk populations**
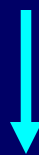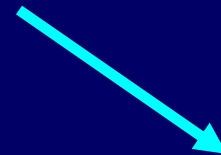
Study Interventions

Eligible participants

⬇

Randomized

⬇

Standard lifestyle recommendations

↙ ↓ ↘

Intensive Lifestyle (n = 1079)   **Metformin (n = 1073)**   **Placebo (n = 1082)**

DPP Population

Asian/Pacific Islander 142 (4%)

American Indian 171 (5%)

Hispanic American 508 (16%)

African American 645 (20%)

Caucasian 1768 (55%)
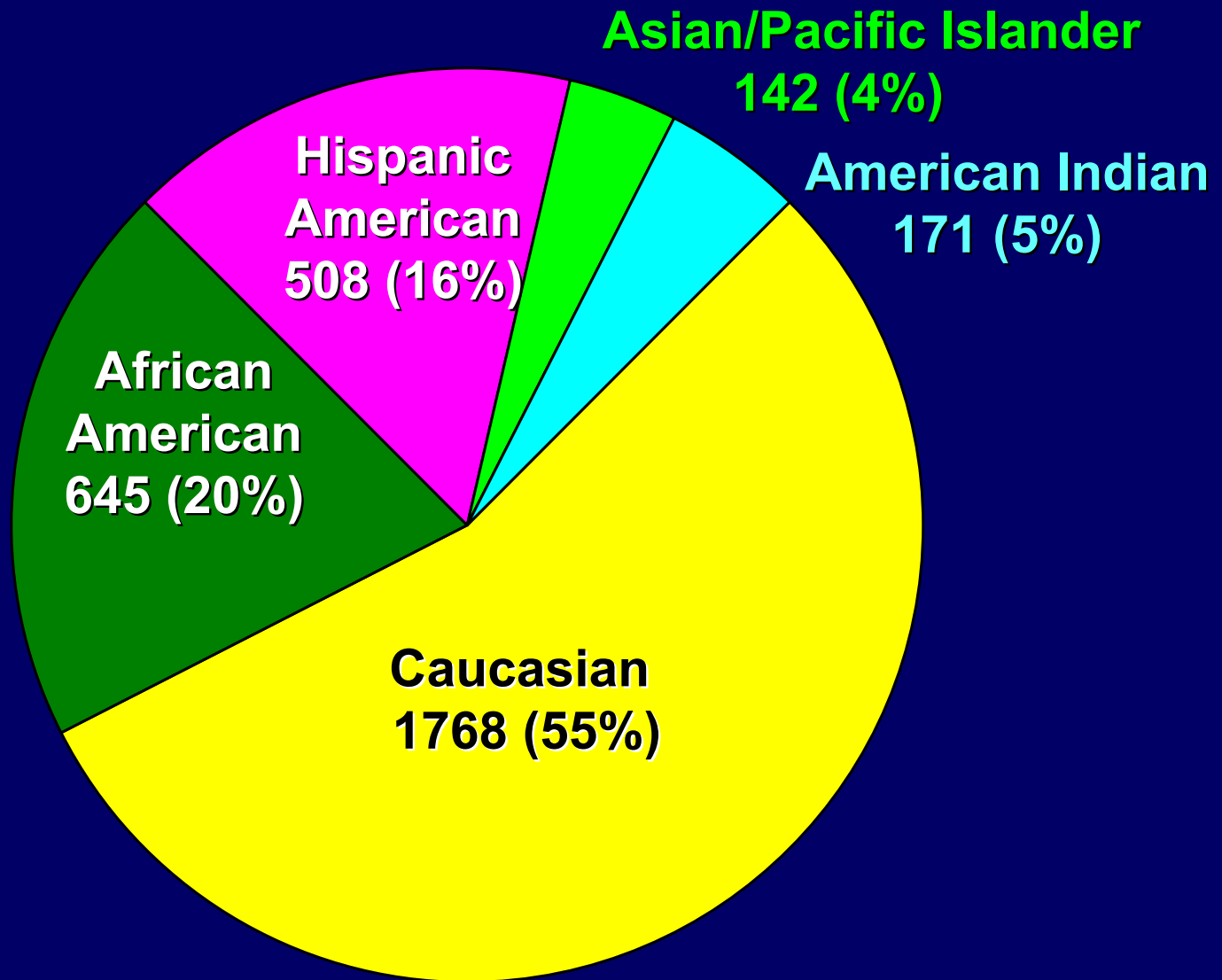
DPP Population

Sex Distribution

Men 32%

Women 68%

Age Distribution

≥ 60 20%

25-44 31%

45-59 49%
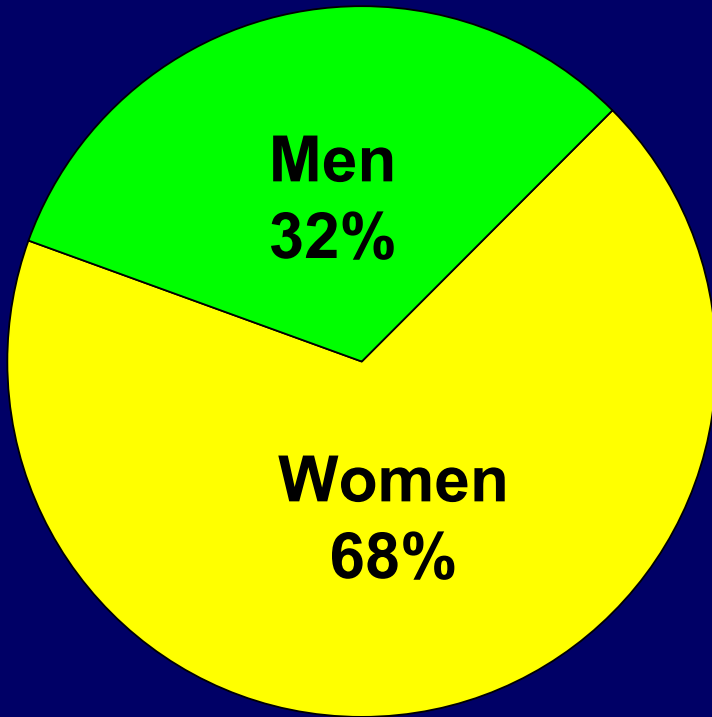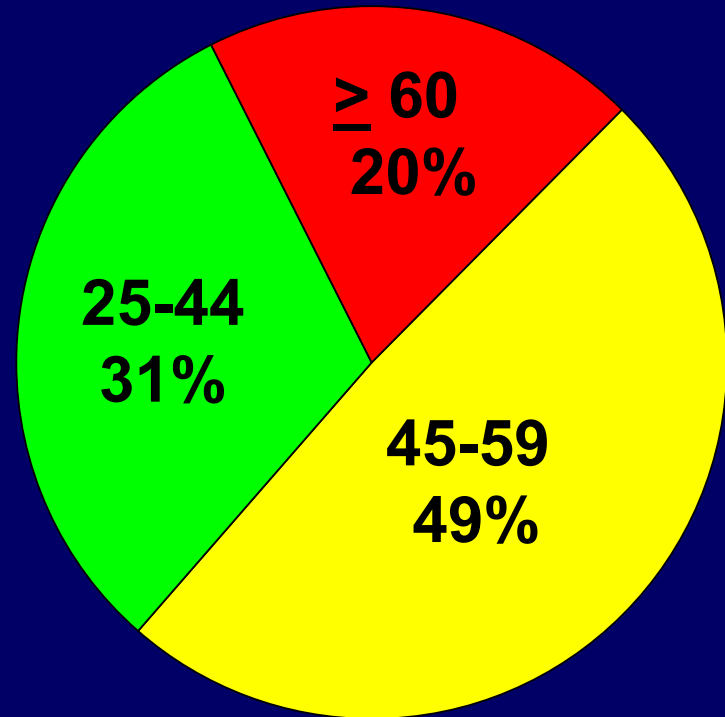
Primary Outcome: Diabetes

- **Annual fasting plasma glucose (FPG) and 75 gm Oral Glucose Tolerance Test**
  - FPG $\geq$ 126 mg/dL, or
  - 2-hr $\geq$ 200 mg/dL
  - Either confirmed with repeat test

- **Semi-annual FPG**
  - $\geq$ 126 mg/dL, confirmed

Lifestyle Intervention

An intensive program with the following specific goals:

- $\geq$ 7% loss of body weight and maintenance of weight loss

  - Dietary fat goal -- <25% of calories from fat
  - Calorie intake goal -- 1200-1800 kcal/day

- $\geq$ 150 minutes per week of physical activity

Interventions: Medications

**Metformin-** 850 mg per day escalating after 4 weeks to 850 mg twice per day

Placebo- Metformin placebo adjusted in parallel with active drugs

Participant Characteristics by Treatment Group Assignment (2)

	Overall	ILS	Metformin	Placebo
n	3,234	1,079	1,073	1,082
FPG (mmol/L) *	5.9 ± 0.5	5.9 ± 0.4	5.9 ± 0.5	5.9 ± 0.5
BMI (kg/m^2)	34.0 ± 6.7	33.9 ± 6.8	33.9 ± 6.6	34.2 ± 6.8
BP (mm Hg)				
Systolic	124 ± 15	124 ± 15	124 ± 15	124 ± 14
Diastolic	78 ± 9	79 ± 9	78 ± 10	78 ± 9

*Mean ± SD

Mean Weight Change

Placebo

Metform[in]

Lifesty[le]

Years from Randomization
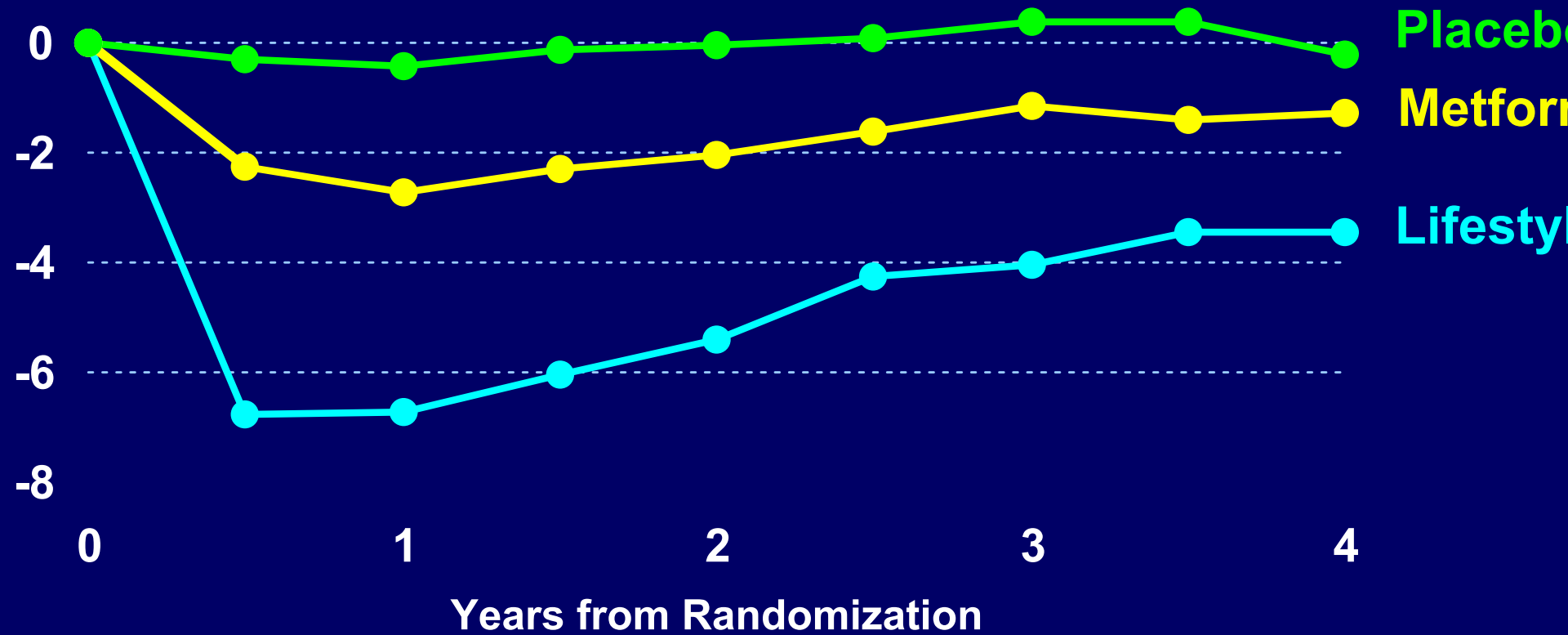
Mean Change in Leisure Physical Activity

Lifestyle

Metformin
Placebo

Years from Randomization
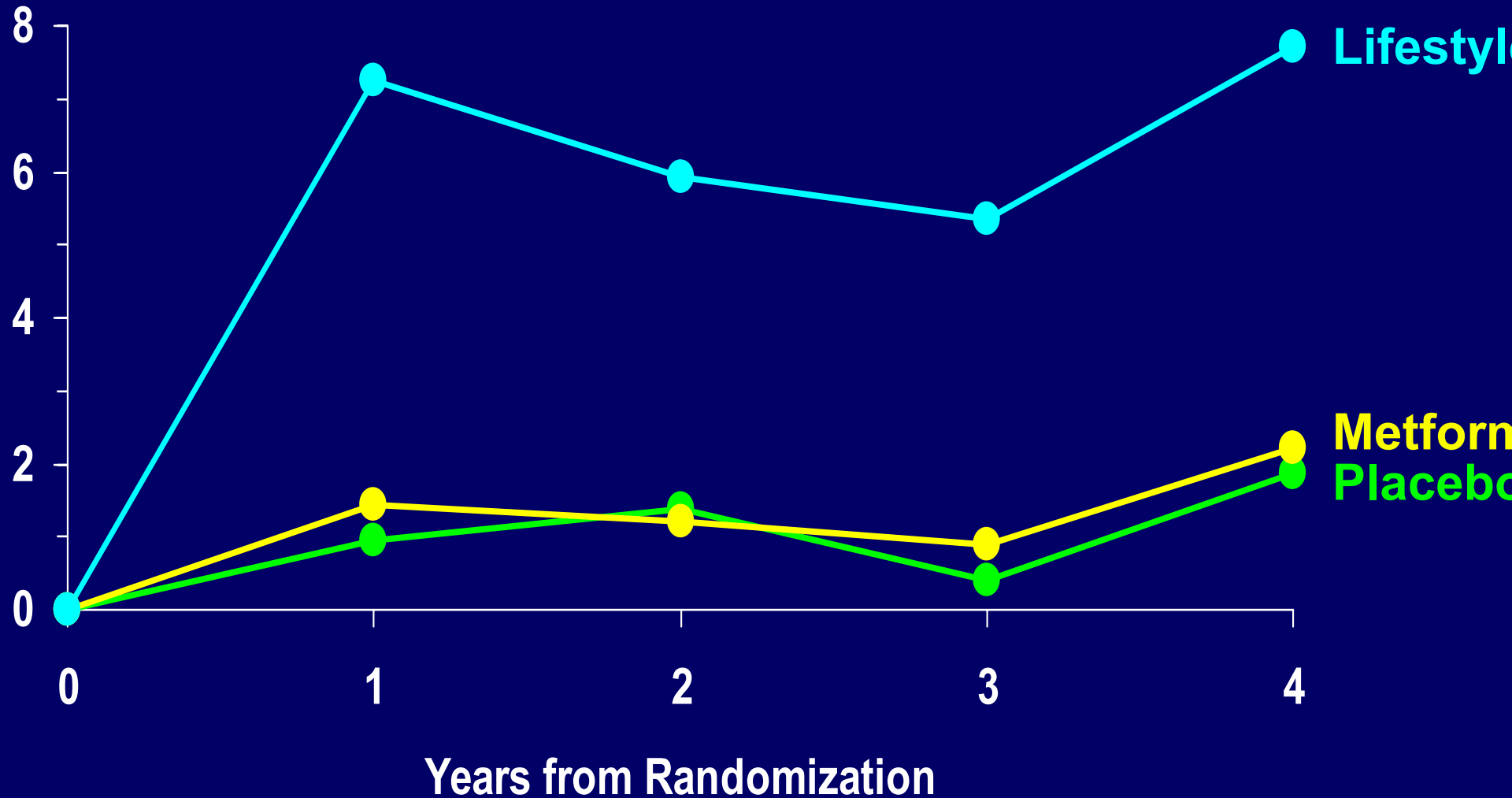
Percent Taking ≥ 80% of Prescribed Dose of Coded Medication
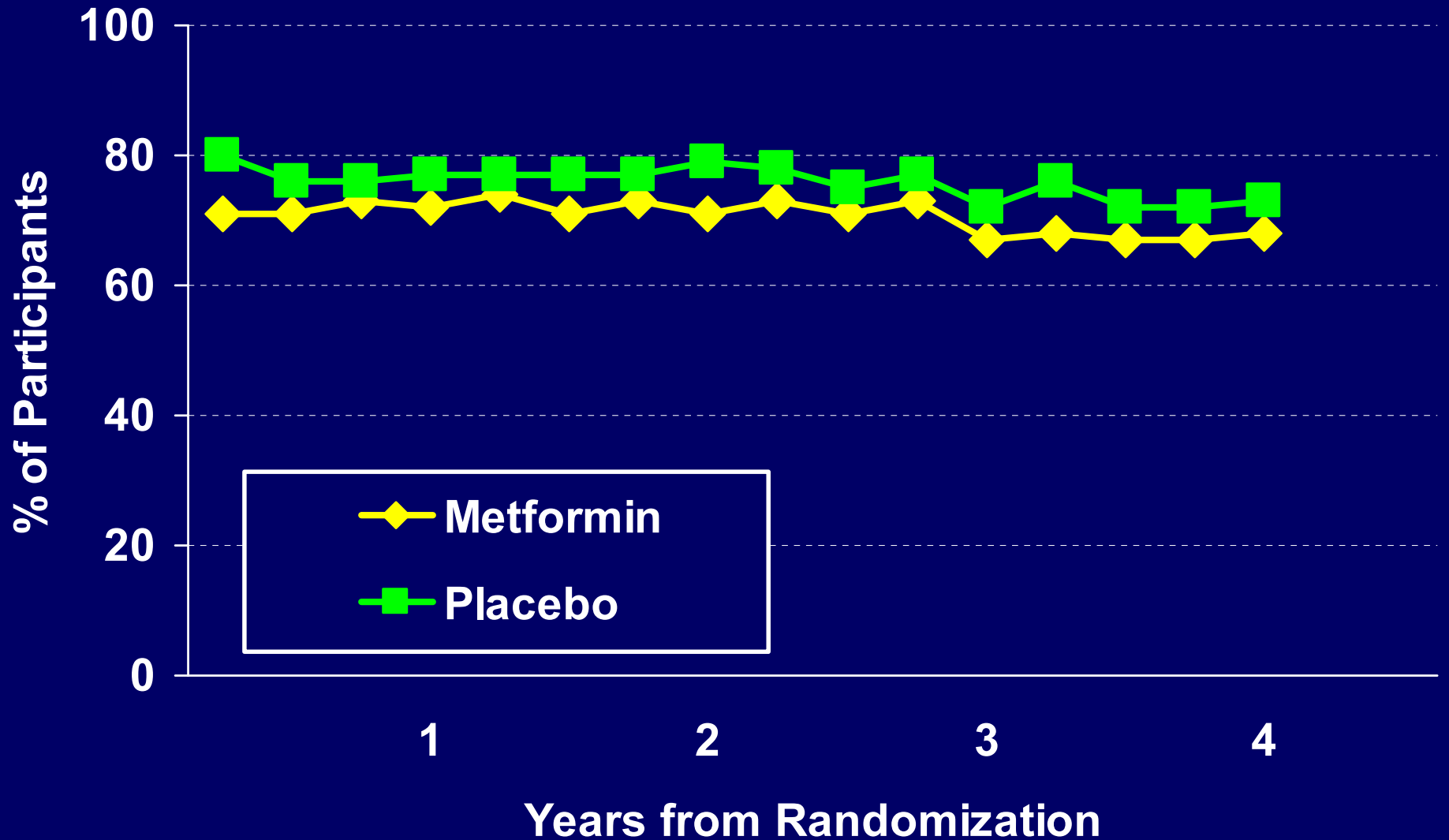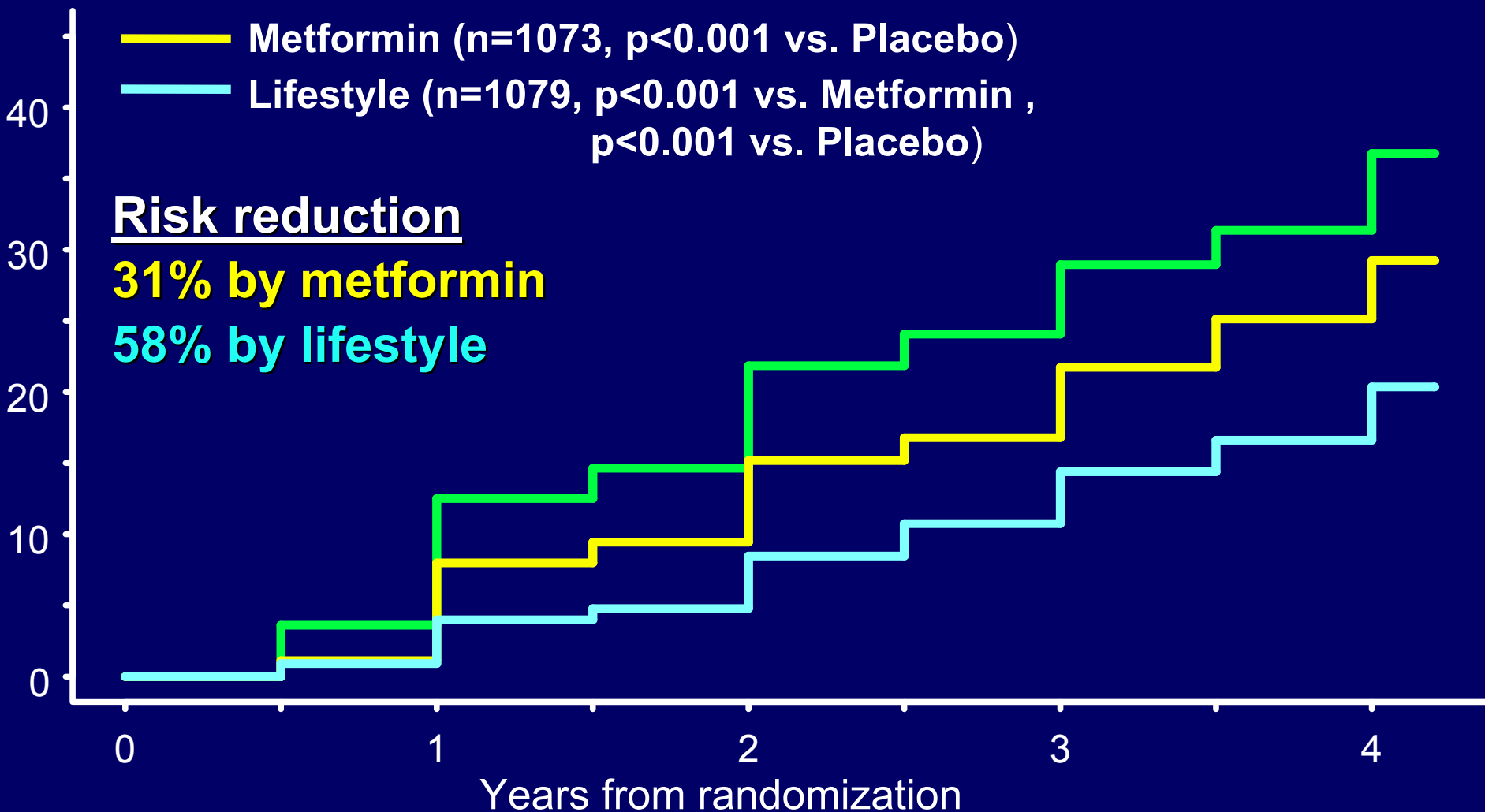
Diabetes Incidence Rates by Sex

Diabetes Incidence Rates by BMI

Legend: Lifestyle, Metformin, Placebo

Y-axis: 0, 4, 8, 12, 16

X-axis: Body Mass Index (kg/m²)

- 24 - < 30 (n=1045)
- 30 - < 35 (n=995)
- ≥ 35 (n=1194)
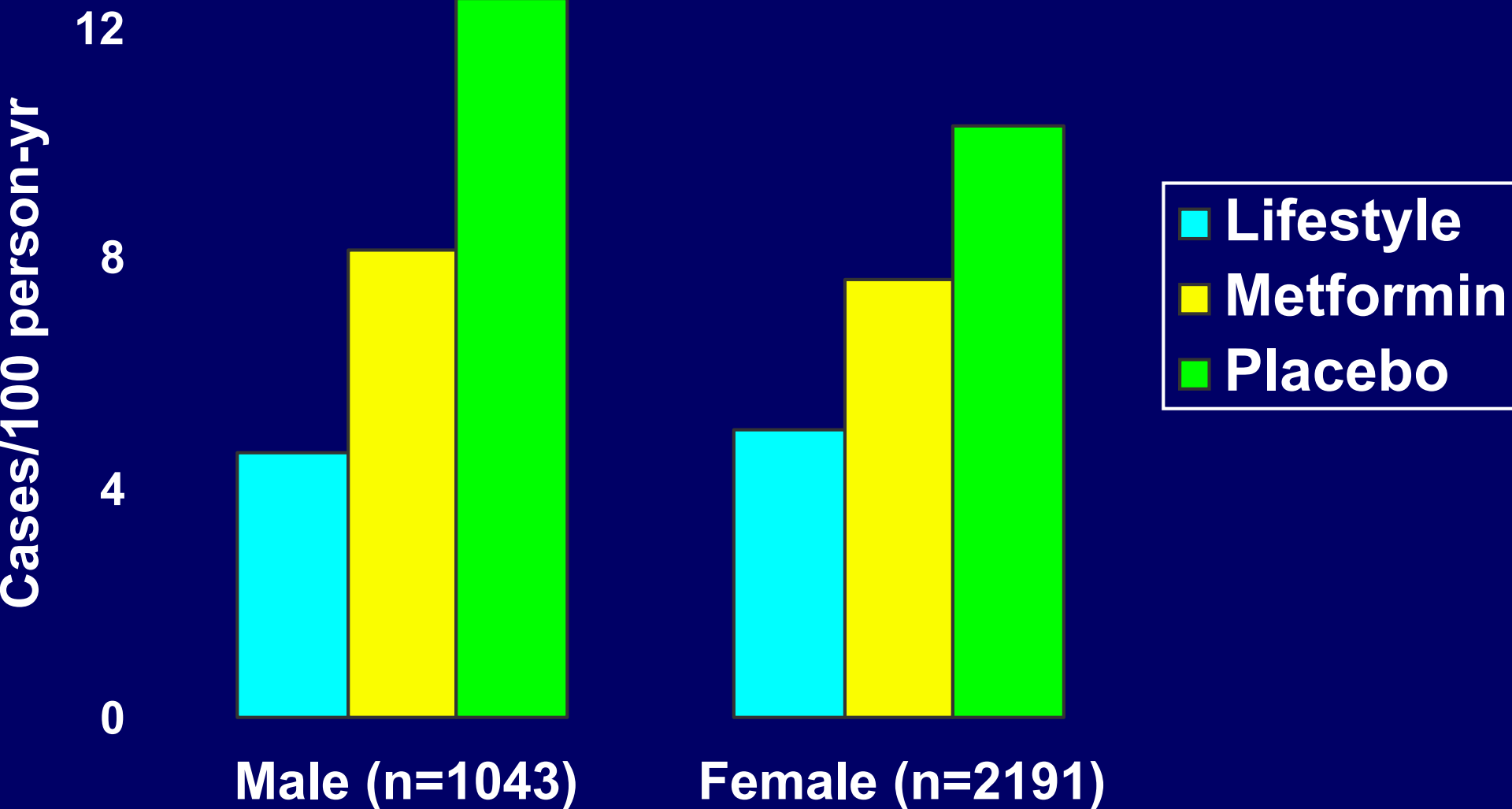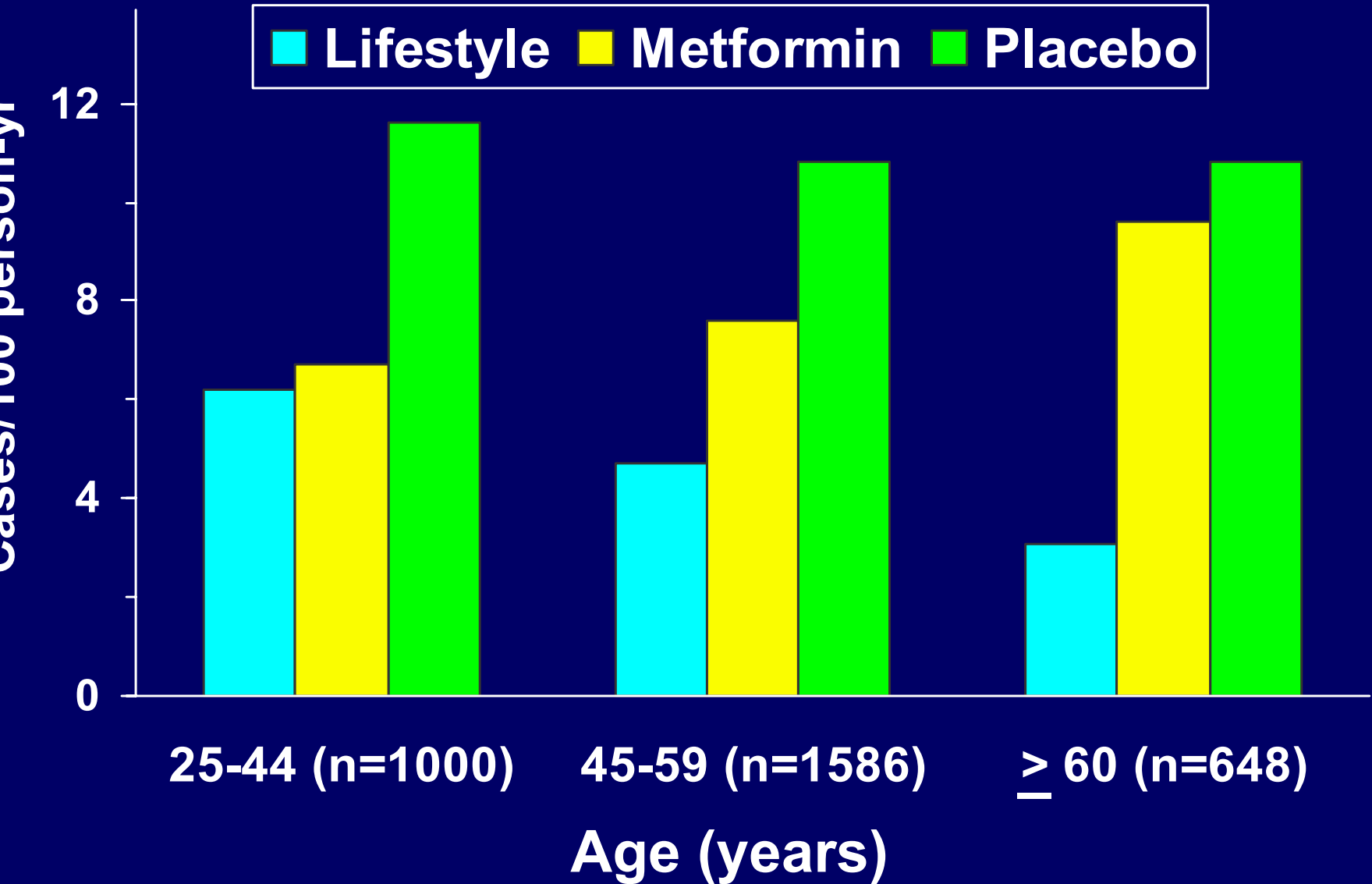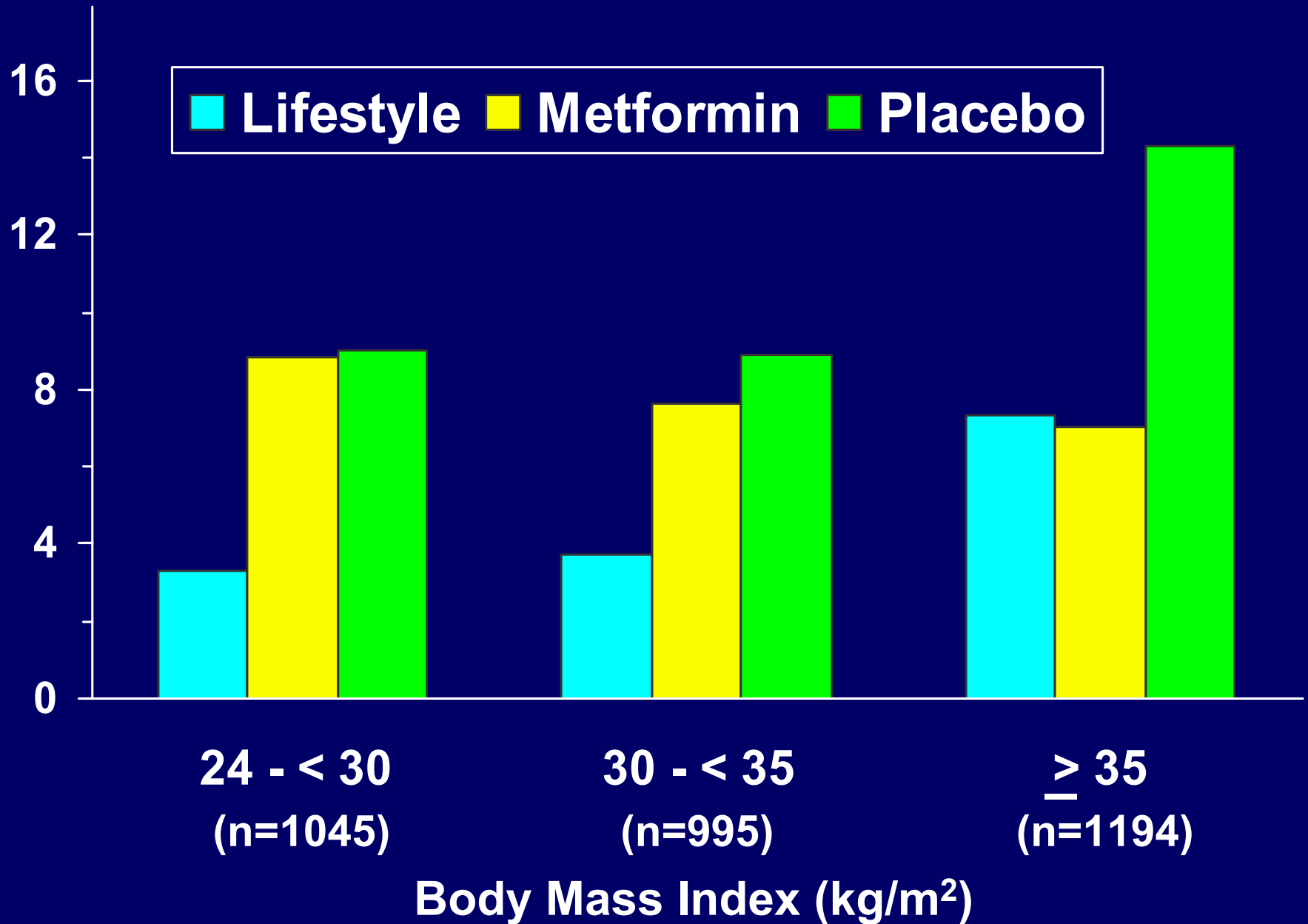
Diabetes Incidence Rates by Fasting Glucose

Cases/100 person yr

Legend:
- Lifestyle
- Metformin
- Placebo

95-109 (5.3- 6.0) (n=2174)

110-125 (6.1-6.9) (n=1060)

Fasting Plasma Glucose: mg/dl (mmol/l)
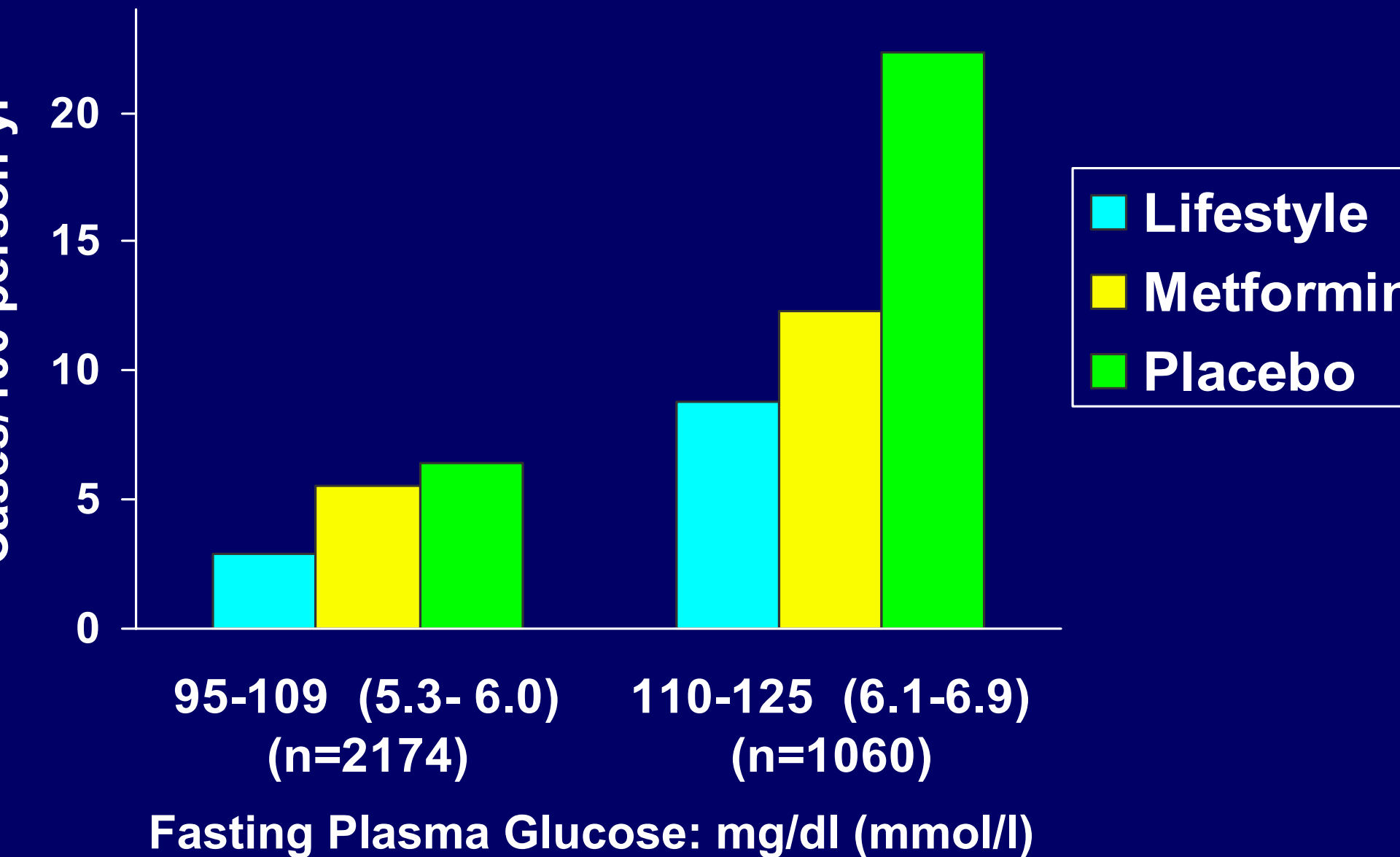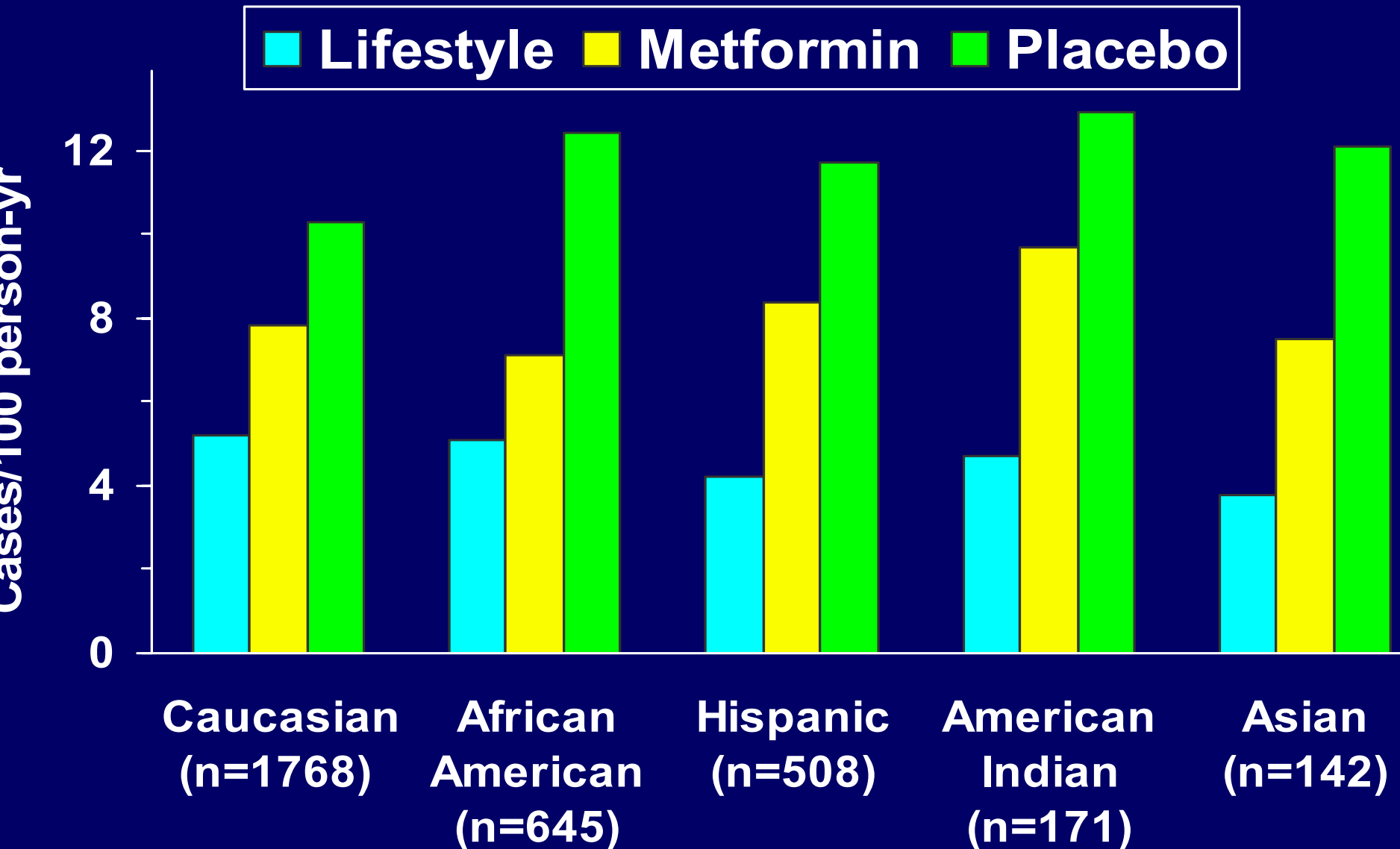
Adverse Events
(rates per 100 person years)

	Placebo	Metformin	Lifestyle
Death	0.16	0.20	0.10
Hospitalization	7.9	8.4	8.0
GI Symptoms	30.7	77.8*	12.9*
Musculoskeletal Symptoms	21.1	20.0	24.1*

* significantly different from placebo

Mean Change in Fasting Plasma Glucose

Placebo

Lifestyle
Metformin

Years from Randomization
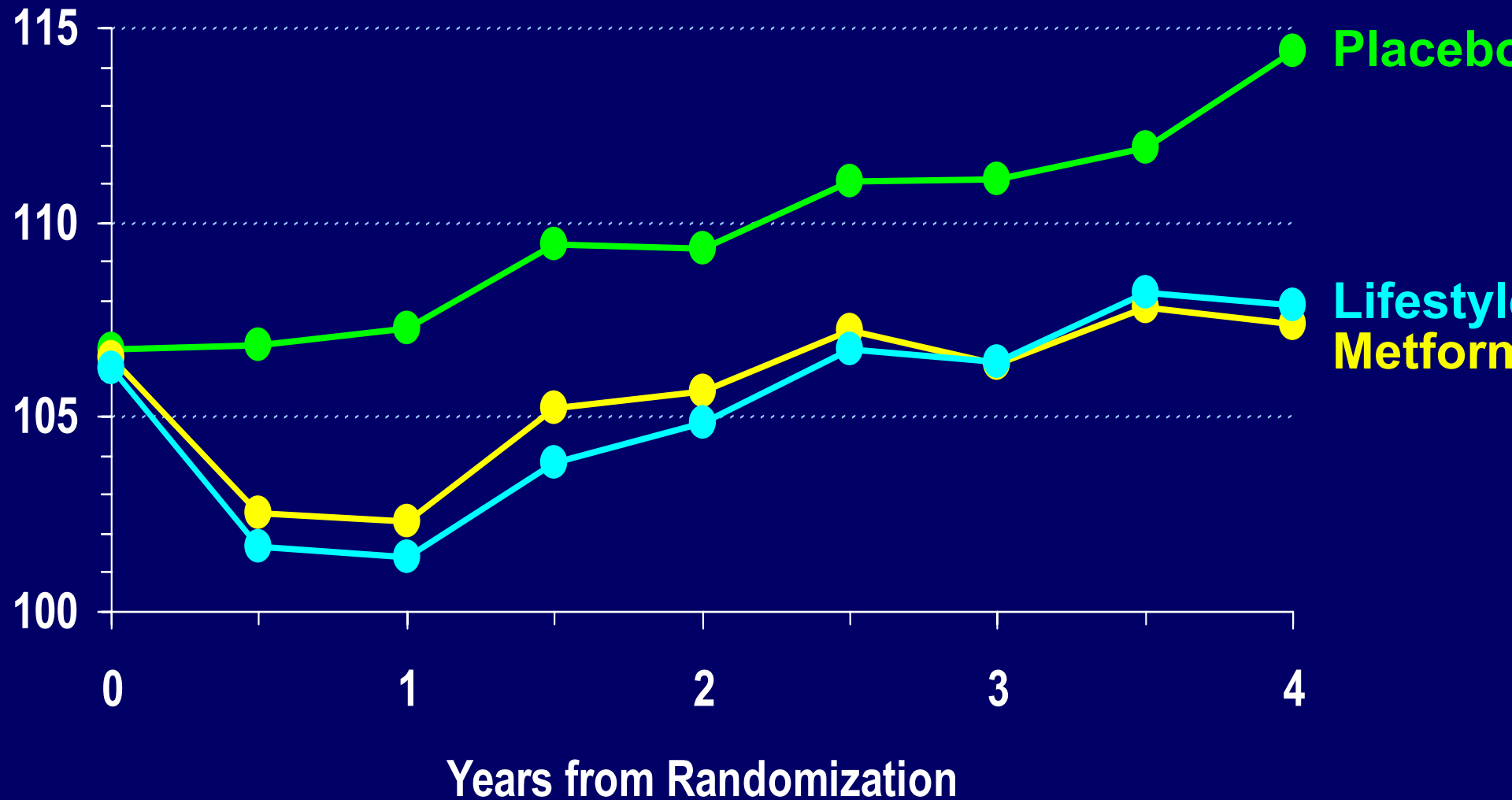
Effect of 1-week withdrawal of Metformin

Table 1—Number and percent with diabetes prior to and including washout

Treatment	Diabetes prior to washout		Diabetes including washout	
	No diabetes	Diabetes	No diabetes	Diabetes
Metformin	668 (74.8)	225 (25.2)	620 (69.4)	273 (30.6)
Placebo	606 (66.6)	304 (33.4)	576 (63.3)	334 (36.7)

Data are n (%).

…. 26% of the effect of metformin to prevent the development of new diabetes can be attributed to an acute pharmacologic effect; after washout, metformin reduced the incidence of diabetes by 25% vs. placebo …

Summary-1

Both interventions were well accepted and safe

Intensive lifestyle resulted in weight loss and increased activity level for the duration of the study

Summary-2

- **Both interventions were effective in men and women and all ethnic groups**

- **Intensive lifestyle intervention was effective in all age groups, including those $\geq$ 60 years of age**

Summary-3

- **Intensive lifestyle intervention reduced the development of diabetes by 58%**

- **Metformin reduced the development of diabetes by 31%**

- **Lifestyle was more effective than metformin**

DPP Secondary Goals

- **Reduce cardiovascular disease (CVD) events**

- **Reduce CVD risk factors**

- **Reduce atherosclerosis**
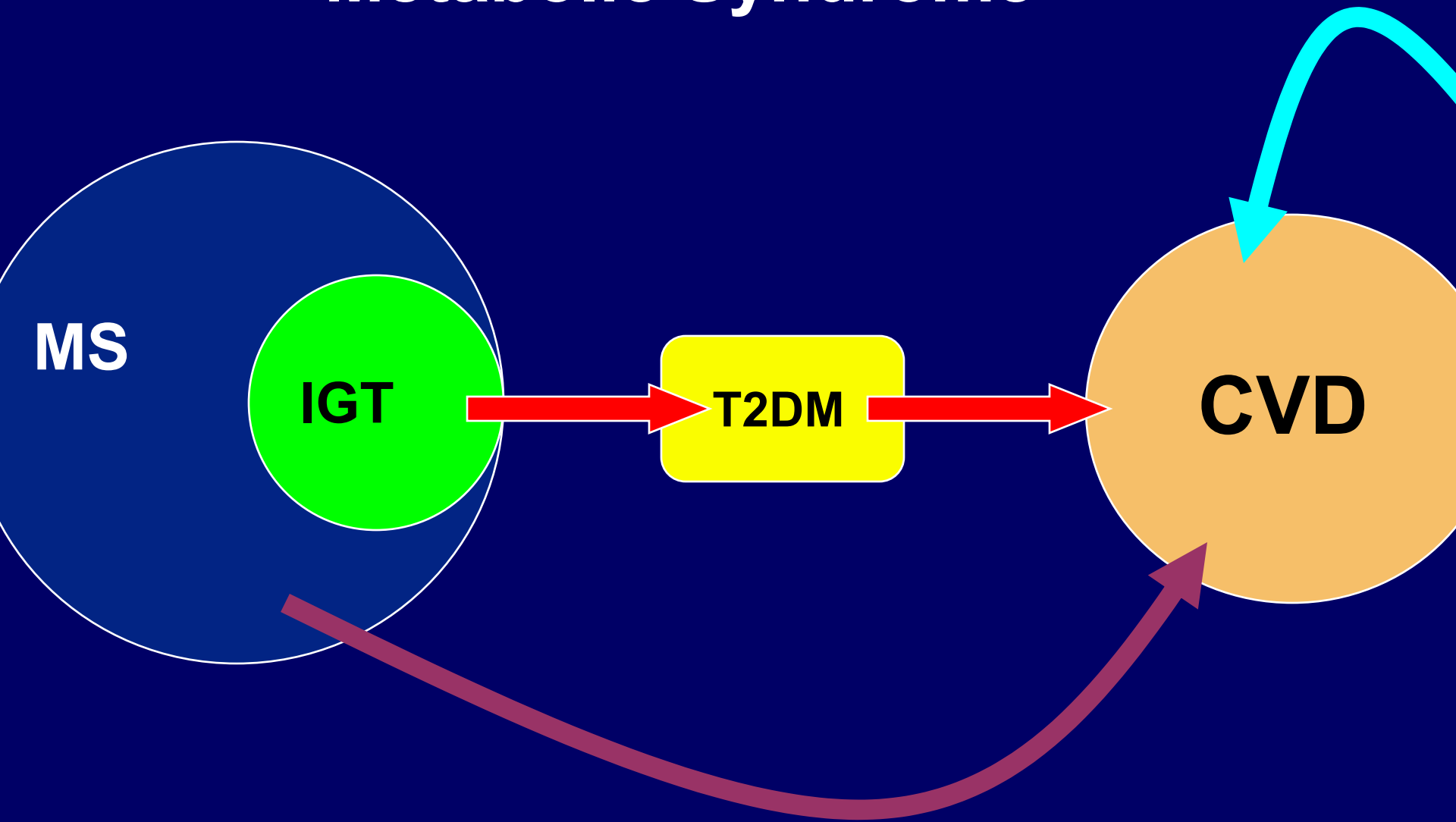
Self-reported Characteristics by Sex and Ethnicity

	Overall	Caucasian	African American	Hispanic	American Indian	Asian American
MEN	1,043	608	165	167	20	83
hx type 2 diabetes *	690 (66%)	390 (64%)	117 (71%)	112 (67%)	13 (65%)	58 (70%)
of high cholesterol	389 (37%)	234 (39%)	65 (39%)	53 (32%)	3 (15%)	34 (41%)
of hypertension	302 (29%)	171 (28%)	58 (35%)	49 (29%)	5 (25%)	19 (23%)
WOMEN	2,191	1,160	480	341	151	59
hx type 2 diabetes	1553 (71%)	799 (69%)	360 (75%)	243 (71%)	116 (77%)	35 (60%)
of gest. diabetes	353 (16%)	191 (17%)	63 (13%)	55 (16%)	36 (24%)	8 (14%)
of high cholesterol	730 (33%)	429 (37%)	147 (31%)	114 (33%)	22 (15%)	17 (29%)
of hypertension	569 (26%)	303 (26%)	144 (30%)	68 (20%)	40 (27%)	15 (26%)

* n, (%)

Diabetes Incidence Rates by 2-hr Glucose
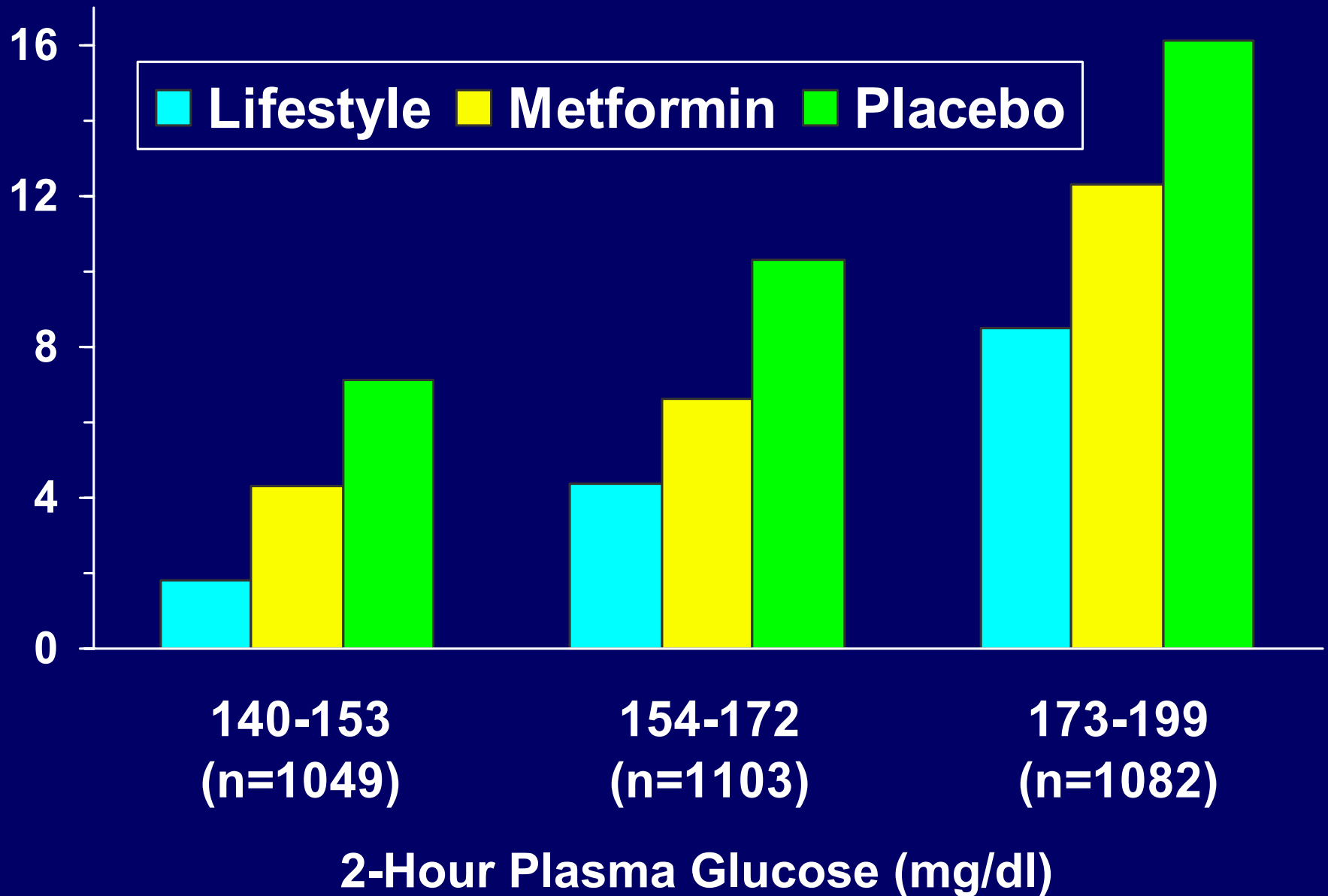
Normal Fasting Glucose at Annual Visits
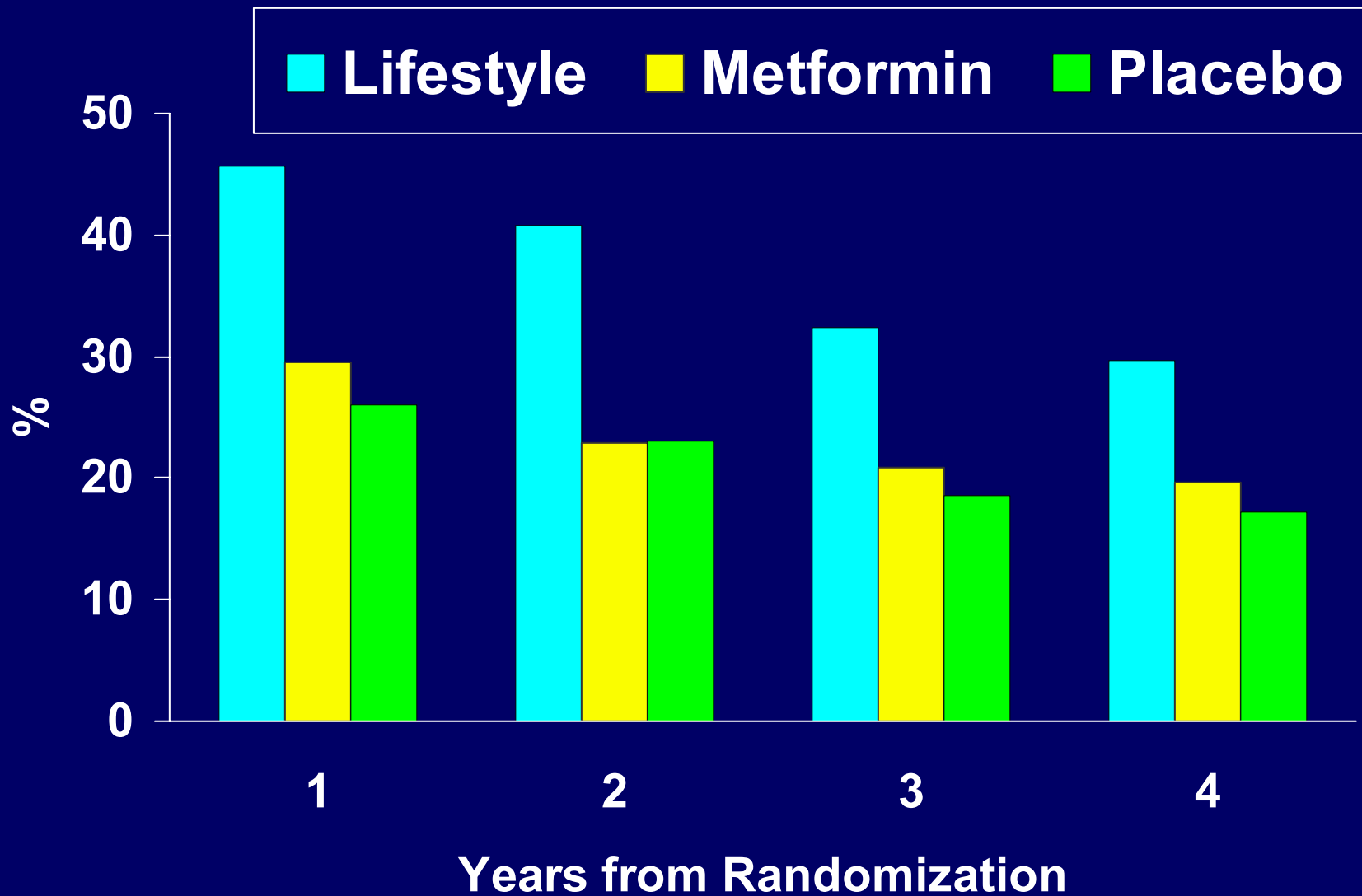
Participant Characteristics by Treatment Group Assignment (1)

	Overall		ILS		Metformin		Placebo
	3,234		1,079		1,073		1,082
Age (years)*	50.6	± 10.7	50.6	± 11.3	50.9	± 10.3	50.3 ± 10.4
Sex**							
Male	1043	(32%)	345	(32%)	363	(34%)	335 (31%)
Female	2191	(68%)	734	(68%)	710	(66%)	747 (69%)
Ethnicity							
Caucasian	1768	(55%)	580	(54%)	602	(56%)	586 (54%)
African-American	645	(20%)	204	(19%)	221	(21%)	220 (20%)
Hispanic	508	(16%)	178	(17%)	162	(15%)	168 (16%)
American Indian	171	(5%)	60	(6%)	52	(5%)	59 (6%)
Asian-American	142	(4%)	57	(5%)	36	(3%)	49 (4%)

*Mean ± SD; ** n, (%)

Demographic and Socioeconomic Characteristics by Sex (1)

	Overall	Male	Female
n	3,234	1,043	2,191
Age (years) *			
25 to <40	505 (16%)	113 (11%)	392 (18%)
40 to <50	1137 (35%)	286 (27%)	851 (39%)
50 to <60	945 (29%)	325 (31%)	620 (28%)
≥60	647 (20%)	319 (31%)	328 (15%)
Race/Ethnicity			
Caucasian	1768 (55%)	608 (58%)	1160 (53%)
African-American	645 (20%)	165 (16%)	480 (22%)
Hispanic	508 (16%)	167 (16%)	341 (16%)
American Indian	171 (5%)	20 (2%)	151 (7%)
Asian American	142 (4%)	83 (8%)	59 (3%)

*** n, (%)**

Demographic and Socioeconomic Characteristics by Sex (2)

	Overall	Male	Female
	3,234	1,043	2,191
Employment Status *			
Employed	2401 (74.2%)	771 (73.9%)	1630 (74.4%)
Retired	420 (13.0%)	217 (20.8%)	203 (9.3%)
Homemaker	204 (6.3%)	1 (0.1%)	203 (9.3%)
Not employed	121 (3.7%)	33 (3.2%)	88 (4.0%)
Seasonally employed	25 (0.8%)	8 (0.8%)	17 (0.8%)
Student	21 (0.6%)	2 (0.2%)	19 (0.9%)
Other	37 (1.1%)	11 (1.1%)	26 (1.2%)
Never worked	5 (0.2%)	0 (0.0%)	5 (0.2%)

n, (%)

Demographic and Socioeconomic Characteristics by Sex (3)

	Overall	Male	Female
	3,234	1,043	2,191
Education in years *			
<13	834 (26%)	221 (21%)	613 (28%)
13 to 16	1556 (48%)	488 (47%)	1068 (49%)
17 or more	844 (26%)	334 (32%)	510 (23%)
Annual family income			
< $20,000	446 (14%)	110 (11%)	336 (15%)
$20,000 to <$35,000	561 (17%)	146 (14%)	415 (19%)
$35,000 to <$50,000	641 (20%)	207 (20%)	434 (20%)
$50,000 to <$75,000	646 (20%)	218 (21%)	428 (20%)
> $75,000	682 (21%)	281 (27%)	401 (18%)
Refused	257 (8%)	81 (8%)	176 (8%)

* n, (%)

Demographic and Socioeconomic Characteristics by Sex (4)

	Overall	Male	Female
n	3,234	1,043	2,191
Marital status *			
Married	1999 (62%)	765 (73%)	1234 (56%)
Divorced	448 (14%)	75 (7%)	373 (17%)
Never married	420 (13%)	115 (11%)	305 (14%)
Widowed	151 (5%)	31 (3%)	120 (6%)
Living together	125 (4%)	31 (3%)	94 (4%)
Separated	91 (3%)	26 (3%)	65 (3%)
Smoking			
Never	1897 (59%)	497 (48%)	1400 (64%)
Former	1111 (34%)	471 (45%)	640 (29%)
Current	226 (7%)	75 (7%)	151 (7%)

*n, (%)

Body Mass Index by Sex and Ethnicity

	Overall	Caucasian	African American	Hispanic	American Indian	Asian American
of MEN	1,043	608	165	167	20	83
BMI (kg/m^2) *	32.0 ± 5.7	32.5 ± 5.8	32.5 ± 6.0	31.7 ± 5.0	31.2 ± 4.1	28.3 ± 3
range	22.7 - 70.9	24.0 - 70.9	24.4 - 64.9	24.4 - 54.4	24.3 - 40.1	22.7 - 44
<30 **	453 (43%)	246 (41%)	66 (40%)	72 (43%)	8 (40%)	61 (74%)
30 to <40	505 (48%)	305 (50%)	84 (51%)	84 (50%)	11 (55%)	21 (25%)
≥40	85 (8%)	57 (9%)	15 (9%)	11 (7%)	1 (5%)	1 (1%)
of WOMEN	2,191	1,160	480	341	151	59
BMI (kg/m^2)	34.9 ± 7.0	35.0 ± 7.1	36.3 ± 7.1	34.0 ± 6.0	33.9 ± 6.3	30.7 ± 6
range	22.1 - 71.5	23.9 - 71.5	24.1 - 65.1	22.6 - 64.9	24.0 - 55.4	22.1 - 50
<30	593 (27%)	325 (28%)	101 (21%)	94 (28%)	38 (25%)	35 (59%)
30 to <40	1134 (52%)	585 (50%)	248 (52%)	194 (57%)	90 (60%)	16 (29%)
≥40	464 (21%)	250 (22%)	131 (27%)	53 (16%)	23 (15%)	7 (12%)

*Mean ± SD; **n, (%)

Glycemia by Sex and Ethnicity

	Overall	Caucasian	African American	Hispanic	American Indian	Asian American
No. of MEN	1,043	608	165	167	20	83
FPG (mmol/L) *	6.0 ± 0.5	6.0 ± 0.5	6.0 ± 0.4	6.0 ± 0.5	5.8 ± 0.4	6.0 ± 0
range	5.2 - 7.7	5.3 - 7.7	5.3 - 7.3	5.3 - 7.7	5.2 - 6.6	5.3 - 7
2-hr PG (mmol/L)	9.1 ± 0.9	9.2 ± 0.9	9.1 ± 1.0	9.1 ± 1.0	9.1 ± 0.9	9.1 ± 0
range	7.8 - 11.0	7.8 - 11.0	7.8 - 11.0	7.8 - 11.0	7.9 - 10.5	7.8 - 11
HbA$_{1c}$ (%)	5.9 ± 0.5	5.8 ± 0.4	6.2 ± 0.7	5.9 ± 0.5	5.8 ± 0.5	6.0 ± 0
range	4.0 - 7.7	4.0 - 7.2	4.2 - 7.7	4.4 - 7.2	4.5 - 6.7	4.8 - 6
> 6.1% **	316 (30%)	133 (22%)	105 (64%)	47 (28%)	5 (25%)	26 (31%)
No. of WOMEN	2,191	1,160	480	341	151	59
FPG (mmol/L)	5.9 ± 0.4	5.9 ± 0.4	6.0 ± 0.5	5.8 ± 0.4	5.5 ± 0.5	5.9 ± 0
range	4.2 - 7.7	5.3 - 7.7	5.3 - 7.5	5.3 - 7.3	4.2 - 6.8	5.3 - 6
2-hr PG (mmol/L)	9.1 ± 0.9	9.2 ± 0.9	9.1 ± 1.0	9.1 ± 0.9	9.1 ± 1.0	9.4 ± 0
range	7.8 - 11.0	7.8 - 11.0	7.8 - 11.0	7.8 - 11.0	7.8 - 11.0	7.8 - 11
HbA$_{1c}$ (%)	5.9 ± 0.5	5.8 ± 0.4	6.2 ± 0.6	5.9 ± 0.5	6 ± 0.4	5.9 ± 0
range	3.2 - 8.5	3.6 - 7.4	3.2 - 8.5	4.4 - 7.5	5.0 - 7.6	4.5 - 7
> 6.1%	616 (28%)	215 (19%)	259 (54%)	76 (22%)	52 (34%)	15 (25%)

*Mean ± SD; **n, (%

Insulinemia by Sex and Ethnicity

ULIN (ol/L)	Overall	Caucasian	African American	Hispanic	American Indian	Asian American
of MEN	1,043	608	165	167	20	83
Fasting *	158 ± 99	157 ± 101	148 ± 74	178 ± 118	151 ± 70	155 ± 8
range	26 - 1104	27 - 684	26 - 510	43 - 1104	48 - 288	36 - 48
30-min	590 ± 423	555 ± 424	527 ± 317	711 ± 414	820 ± 760	661 ± 44
range	27 - 4854	31 - 4854	66 - 1812	27 - 2190	294 - 3480	78 - 228
of WOMEN	2,191	1,160	480	341	151	59
Fasting	158 ± 86	151 ± 80	167 ± 91	168 ± 91	170 ± 89	148 ± 10
range	14 - 720	14 - 552	18 - 576	32 - 720	34 - 534	36 - 57
30-min	607 ± 368	557 ± 323	617 ± 416	681 ± 378	810 ± 444	569 ± 27
range	18 - 3600	36 - 3600	18 - 3024	52 - 2100	78 - 2436	132 - 124

*Mean ± SD

Lipids by Sex and Ethnicity

ids (mmol/L)	Overall	Caucasian	African American	Hispanic	American Indian	Asian American
of MEN	1,043	608	165	167	20	83
Total cholesterol *	5.2 ± 0.9	5.2 ± 0.9	5.2 ± 0.9	5.2 ± 0.9	4.9 ± 1.0	5.4 ± 1.0
HDL cholesterol	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	1.1 ± 0.2
LDL cholesterol	3.3 ± 0.8	3.2 ± 0.8	3.4 ± 0.9	3.2 ± 0.9	2.9 ± 1.0	3.4 ± 0.8
Trigylcerides	2.0 ± 1.1	2.1 ± 1.1	1.5 ± 0.9	2.2 ± 1.2	2.1 ± 1.1	2.0 ± 1.1
of WOMEN	2,191	1,160	480	341	151	59
Total cholesterol	5.3 ± 1.0	5.4 ± 0.9	5.2 ± 1.0	5.2 ± 0.9	4.8 ± 1.0	5.4 ± 0.9
HDL cholesterol	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3
LDL cholesterol	3.2 ± 0.9	3.2 ± 0.8	3.3 ± 0.9	3.2 ± 0.9	2.8 ± 0.8	3.2 ± 0.9
Trigylcerides	1.7 ± 0.9	1.9 ± 1.0	1.2 ± 0.6	1.8 ± 0.9	1.7 ± 0.8	2.0 ± 1.2

*Mean ± SD