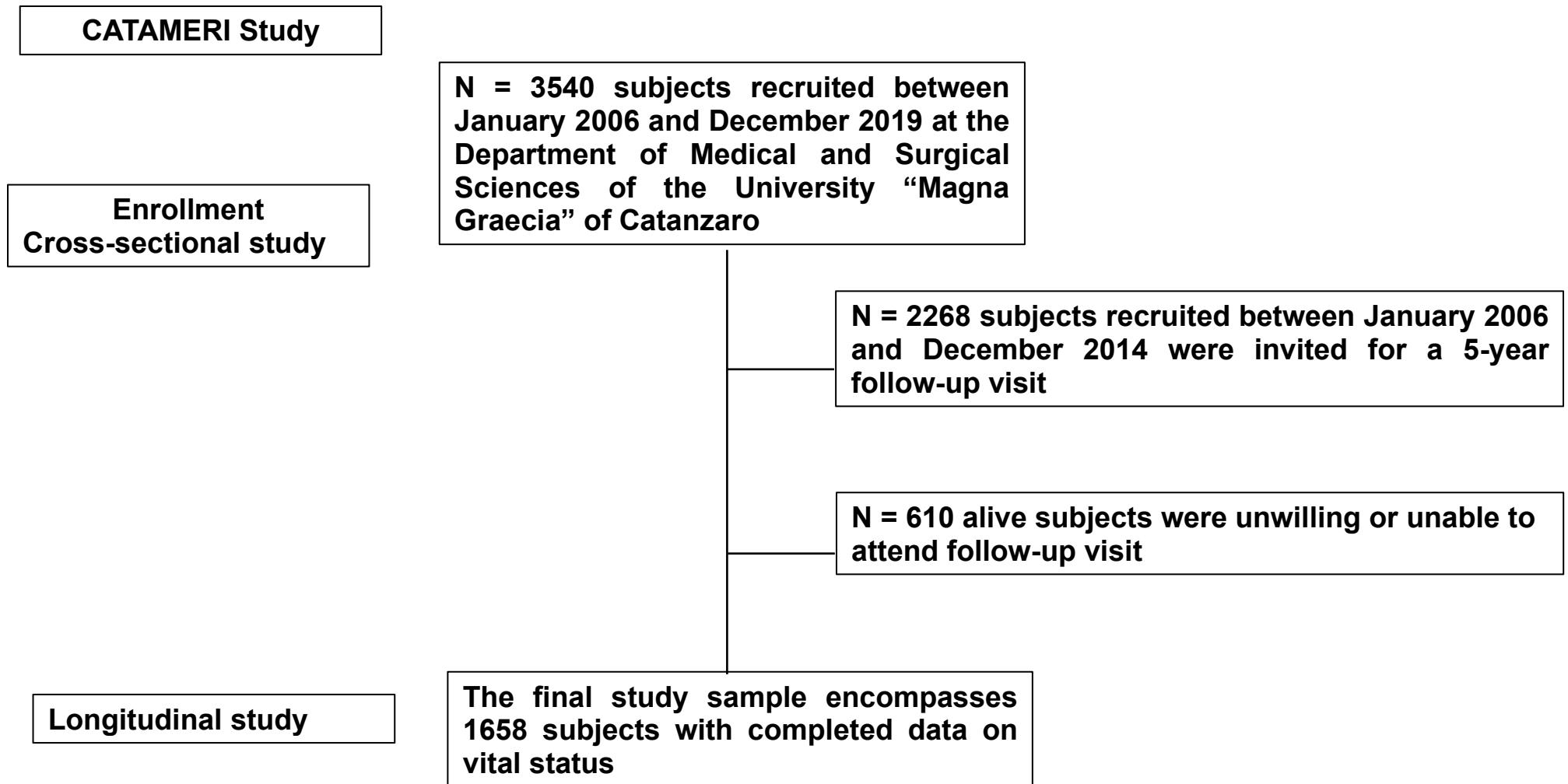


Supplemental Figure 1: Flowchart of the study population



Supplemental Table S1—Differences in baseline characteristics of men and women with NGT, prediabetes, and type 2 diabetes

		Women		Prediabetes vs. NGT	Diabetes vs. NGT		Men		Prediabetes vs. NGT	Diabetes vs. NGT
	NGT (n=524)	Prediabetes (n=540)	Diabetes (n=576)	P value§	P value§	NGT (n=406)	Prediabetes (n=648)	Diabetes (n=846)	P value§	P value§
Age (yrs)	52±9	57±10	63±10	<0.0001	<0.0001	52±9	57±9	61±10	<0.0001	<0.0001
BMI (kg/m^2)	29.7±6.3	31.1±6.6	32.0±7.0	<0.0001	<0.0001	28.7±4.3	30.4±5.4	30.1±5.2	<0.0001	<0.0001
Waist circumference (cm)	98±14	102±14	104±15	<0.0001	<0.0001	100±10	105±13	105±13	<0.0001	<0.0001
Current smokers (%)	15.3	12.2	5.6	0.20	<0.0001	28.3	21.5	22.0	0.01	0.01
Systolic blood pressure (mmHg)	129±17	132±17	142±20	0.21	<0.0001	134±15	135±17	137±18	0.95	0.20
Diastolic blood pressure (mmHg)	79±10	79±10	81±11	0.46	0.001	84±10	83±10	81±11	0.34	0.06
Total cholesterol (mg/dl)	206±37	209±41	196±42	0.19	0.001	203±38	195±39	180±43	0.05	<0.0001
LDL cholesterol (mg/dl)	130±34	134±36	117±37	0.17	<0.0001	134±32	125±34	105±39	0.10	<0.0001
HDL (mg/dl)	58±13	54±13	50±14	<0.0001	<0.0001	46±12	46±13	43±12	0.38	<0.0001
Triglycerides (mg/dl)	110±59	134±67	149±80	<0.0001	<0.0001	141±78	143±85	159±101	0.19	<0.0001
Fasting Glucose (mg/dL)	87±6	98±10	157±63	<0.0001	<0.0001	89±6	101±10	151±48	<0.0001	<0.0001

2-h glucose (mg/dl)	106±19	141±29	226±39*	<0.0001	<0.0001	104±19	139±31	228±46**	<0.0001	<0.0001
HbA1c (%/mmol/mol)	5.3±0.2 (34±1.4)	5.7±0.3 (39±2.2)	7.6±1.6 (60±11)	<0.0001	<0.0001	5.3±0.2 (34±1.4)	5.7±0.3 (39±2.2)	7.3±1.6 (56±9.9)	<0.0001	<0.0001
Fasting Insulin (μ U/ml)	11±6	15±8	18±13	<0.0001	<0.0001	11±6	15±8	18±13	<0.0001	<0.0001
HOMA-IR	2.4±1.5	3.6±2.3	6.8±5.9	<0.0001	<0.0001	2.4±1.5	3.6±2.3	6.8±5.9	<0.0001	<0.0001
hsCRP (mg/l)	3.7±2.5	4.7±3.7	6.1±4.4	<0.0001	<0.0001	3.1±2.7	3.2±2.0	4.3±3.1	0.73	<0.0001
Fibrinogen (mg/dl)	325±70	333±77	370±96	0.64	<0.0001	300±76	306±79	338±89	0.95	<0.0001
White blood cell count (cell/mm ³)	6452±1755	6766±1843	7713±2204	0.007	<0.0001	6972±1872	7037±1892	7451±2116	0.46	<0.0001
ACE inhibitor /angiotensin II receptor blocker therapy (%)	35.7	46.5	68.2	0.004	<0.0001	36.9	51.5	60.4	<0.0001	<0.0001
Beta blockers therapy (%)	15.5	23.9	28.5	0.0007	<0.0001	12.6	20.5	25.7	0.001	<0.0001
Diuretics (%)	16.4	30.4	44.4	<0.0001	<0.0001	11.8	24.7	30.4	<0.0001	<0.0001
Calcium channel blockers (%)	13.0	13.1	22.9	0.99	<0.0001	14.8	17.7	23.5	0.24	0.0005
Antiplatelet therapy (%)	8.0	11.3	33.2	0.08	<0.0001	12.1	17.4	37.6	0.02	<0.0001
Lipid-lowering therapy (%)	10.1	13.7	36.1	0.08	<0.0001	10.1	22.4	41.0	<0.0001	<0.0001
Non-insulin therapy (%)	---	---	47.9	---	---	--	--	46.8	---	---

Insulin therapy (%)	---	---	25.8	---	---	--	--	21.5	---	---
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Data are means±SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between the three groups of glucose tolerance were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons. $^{\$}$ P values refer to results after analyses with adjustment for age. Insulin, triglycerides, and hsCRP levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale.

*Number=89 subjects

**Number= 171 subjects

Supplemental Table S2 - Logistic regression analyses of the association between CHD and cerebrovascular disease across the three glucose tolerance groups stratified by sex

	CHD										Cerebrovascular disease									
					Age-adjusted			Full adjusted§						Age-adjusted			Full adjusted§			
Study groups	Relative risk	95%CI	P	OR	95%CI	P	OR	95%CI	P	Relative risk	95%CI	P	OR	95%CI	P	OR	95%CI	P		
Women																				
NGT (reference)	1	---	---	1	---	---	1	---	---	1	---	---	1	---	---	1	---	1	---	
Prediabetes	1.94	0.83-4.49	0.12	1.51	0.63-3.61	0.34	1.03	0.33-3.14	0.95	4.85	0.56-41.39	0.14	4.01	0.46-34.91	0.20	2.10	0.20-22.03	0.53		
Type 2 diabetes	9.21	4.49-18.86	<0.0001	6.10	2.80-13.18	<0.0001	3.06	1.03-9.06	0.04	12.7	1.68-95.52	0.01	8.40	1.03-68.13	0.04	3.35	0.30-37.66	0.32		
Men																				
NGT (reference)	1	---	---	1	---	---	1	---	---	1	---	---	1	---	---	1	---	1	---	
Prediabetes	2.11	1.32-3.39	0.001	1.83	1.10-3.05	0.02	1.31	0.66-2.59	0.43	0.93	0.26-3.31	0.92	0.76	0.20-2.67	0.64	0.32	0.02-5.09	0.57		
Type 2 diabetes	5.25	3.41-8.08	<0.0001	4.71	2.92-7.59	<0.0001	2.68	1.38-5.21	0.004	1.67	0.55-5.07	0.35	1.07	0.33-3.47	0.90	0.50	0.02-6.44	0.92		

§ Logistic regression model including age, BMI, smoking status, systolic and diastolic blood pressure, total, LDL and HDL cholesterol, triglycerides, HOMA-IR index, hsCRP, fibrinogen, and white blood cell count.

CHD: myocardial infarction, percutaneous or surgical coronary revascularization procedures. OR, odds ratio; CI: confidence interval

Supplemental Table S3—Differences in baseline characteristics of the longitudinal cohort between men and women with NGT, prediabetes, and type 2 diabetes

	NGT			Prediabetes			Diabetes		
	Women (n=410)	Men (n=349)	P value	Women (n=231)	Men (n=272)	P value	Women (n=162)	Men (n=234)	P value
Age (yrs)	46±13	48±13	0.051	55±12	52±12	0.02	62±10	59±10	0.03
BMI (kg/m^2)	29.2±6.7	28.8±4.4	0.34	31.0±5.8	30.5±5.5	0.36	31.9±5.9	30.5±5.2	0.01
Waist circumference (cm)	96±15	100±10	<0.0001	101±14	104±12	0.01	105±13	105±12	0.94
Current smokers (%)	16.5	28.0	<0.0001	12.6	22.0	0.007	5.0	21.8	<0.0001
Systolic blood pressure (mmHg)	128±18	136±15	<0.0001	133±16	137±16	<0.0001	143±19	137±16	0.003
Diastolic blood pressure (mmHg)	79±11	85±10	<0.0001	81±10	85±10	<0.0001	81±11	83±11	0.94
Total cholesterol (mg/dl)	201±38	203±36	0.49	216±41	200±36	<0.0001	195±43	181±42	0.001
LDL (mg/dl)	121±33	133±32	<0.0001	136±37	129±32	0.058	116±36	104±37	0.01
HDL (mg/dl)	57±14	46±12	<0.0001	54±12	44±11	<0.0001	48±12	42±11	<0.0001
Triglycerides (mg/dl)	103±52	142±83	<0.0001	138±71	154±106	0.08	157±87	158±83	0.90
Fasting Glucose (mg/dL)	86±7	88±6	<0.0001	100±11	102±9	0.03	158±65	150±56	0.20
2-h glucose (mg/dl)	101±19	104±19	0.18	143±28	135±31	0.007	229±34*	230±55**	0.92
HbA1c % (mmol/mol)	5.2±0.3 (33±1.8)	5.3±0.2 (34±1.2)	0.52	5.7±0.4 (39±2.4)	5.6±0.3 (38±1.8)	0.81	7.5±1.8 (58±11)	7.3±1.5 (56±9.3)	0.28

hsCRP (mg/l)	3.6±2.3	3.4±2.6	0.86	4.8±3.4	3.7±2.9	0.001	6.4±4.5	3.4±2.2	<0.0001
Fibrinogen (mg/dl)	316±69	301±73	0.004	336±72	311±90	0.001	360±82	330±75	0.001
White blood cell count (cell/mm ³)	6758±1846	7081±1888	0.02	7089±2058	7106±1980	0.92	7989±2193	7517±1974	0.04
ACE inhibitor /angiotensin II receptor blocker therapy (%)	38.3	44.1	0.11	58.3	59.7	0.74	77.0	71.6	0.22
Beta blockers therapy (%)	16.0	8.9	0.004	24.8	18.3	0.07	36.0	30.6	0.26
Diuretics (%)	15.3	16.1	0.74	34.3	25.6	0.03	47.8	36.6	0.02
Calcium channel blockers (%)	10.4	16.7	0.01	17.4	19.8	0.49	23.6	25.9	0.61
Antiplatelet therapy (%)	8.2	11.5	0.12	16.1	21.6	0.11	37.9	47.4	0.07
Lipid-lowering therapy (%)	9.7	10.1	0.86	19.6	23.1	0.33	52.2	59.9	0.13
Non-Insulin therapy (%)	---	--	---	---	--	---	42.9	53.8	0.03
Insulin therapy (%)	---	--	---	---	--	---	31.7	23.5	0.07
Number of incident major adverse outcome (%)	21 (5.1)	31 (8.9)	0.03	17 (7.4)	21 (7.7)	0.89	43 (26.5)	57 (24.4)	0.63

Data are means±SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between women and men were performed using unpaired Student's t test. Insulin, triglycerides, and hsCRP levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale.

*Number=31 subjects

**Number= 56 subjects

Supplemental Table S4—Differences in baseline characteristics of the longitudinal cohort between men and women with NGT, prediabetes, and type 2 diabetes

		Women		Prediabetes vs. NGT	Diabetes vs. NGT		Men		Prediabetes vs. NGT	Diabetes vs. NGT
	NGT (n=410)	Prediabetes (n=231)	Diabetes (n=162)	P value§	P value§	NGT (n=349)	Prediabetes (n=272)	Diabetes (n=234)	P value§	P value§
Age (yrs)	46±13	55±12	62±10	<0.0001#	<0.0001#	48±13	52±12	59±10	<0.0001#	<0.0001#
BMI (kg/m^2)	29.2±6.7	31.0±5.8	31.9±5.9	0.001	<0.0001	28.8±4.4	30.5±5.5	30.5±5.2	<0.0001	<0.0001
Waist circumference (cm)	96±15	101±14	105±13	0.001	<0.0001	100±10	104±12	105±12	<0.0001	<0.0001
Current smokers (%)	16.5	12.6	5.0	0.23	0.0004	28.0	22.0	21.8	0.10	0.11
Systolic blood pressure (mmHg)	128±18	133±16	143±19	0.62	<0.0001	136±15	137±16	137±16	0.56	0.93
Diastolic blood pressure (mmHg)	79±11	81±10	81±11	0.50	0.47	85±10	85±10	83±11	0.79	0.23
Total cholesterol (mg/dl)	201±38	216±41	195±43	0.002	0.001	203±36	200±36	181±42	0.20	<0.0001
LDL (mg/dl)	121±33	136±37	116±36	0.01	0.004	133±32	129±32	104±37	0.29	<0.0001
HDL (mg/dl)	57±14	54±12	48±12	0.001	<0.0001	46±12	44±11	42±11	0.04	<0.0001
Triglycerides (mg/dl)	103±52	138±71	157±87	<0.0001	<0.0001	142±83	154±106	158±83	0.43	0.21
Fasting Glucose (mg/dL)	86±7	100±11	158±65	<0.0001	<0.0001	88±6	102±9	150±56	<0.0001	<0.0001
2-h glucose (mg/dl)	101±19	143±28	229±34*	<0.0001	<0.0001	104±19	135±31	230±55**	<0.0001	<0.0001

HbA1c (%/mmol/mol)	5.2±0.3 (33±2.1)	5.7±0.4 (39±2.8)	7.5±1.8 (58±10)	<0.0001	<0.0001	5.3±0.2 (34±1.2)	5.6±0.3 (38±1.8)	7.3±1.5 (56±9.3)	<0.0001	<0.0001
hsCRP (mg/l)	3.6±2.3	4.8±3.4	6.4±4.5	0.003	<0.0001	3.4±2.6	3.7±2.9	3.4±2.2	0.34	0.27
Fibrinogen (mg/dl)	316±69	336±72	360±82	0.05	<0.0001	301±73	311±90	330±75	0.63	0.04
White blood cell count (cell/mm ³)	6758±1846	7089±2058	7989±2193	0.01	<0.0001	7081±1888	7106±1980	7517±1974	0.59	<0.0001
ACE inhibitor /angiotensin II receptor blocker therapy (%)	38.3	58.3	77.0	<0.0001	<0.0001	44.1	59.7	71.6	0.0002	<0.0001
Beta blockers therapy (%)	16.0	24.8	36.0	0.37	0.0007	8.9	18.3	30.6	0.009	<0.0001
Diuretics (%)	15.3	34.3	47.8	<0.0001	<0.0001	16.1	25.6	36.6	0.004	<0.0001
Calcium channel blockers (%)	10.4	17.4	23.6	0.01	<0.0001	16.7	19.8	25.9	0.38	0.01
Antiplatelet therapy (%)	8.2	16.1	37.9	0.003	<0.0001	11.5	21.6	47.4	0.001	<0.0001
Lipid-lowering therapy (%)	9.7	19.6	52.2	0.0006	<0.0001	10.1	23.1	59.9	<0.0001	<0.0001
Non-Insulin therapy (%)	---	---	42.9	---	---	--	--	53.8	---	---
Insulin therapy (%)	---	---	31.7	---	---	--	--	23.5	---	---

Data are means±SD, unless otherwise indicated. Categorical variables were compared by χ^2 test. Comparisons between the three groups of glucose tolerance were performed using a general linear model with post hoc Fisher's least significant difference correction for pairwise comparisons. §P values refer to results after analyses with adjustment for age. # Non adjusted P value. Insulin, triglycerides, and hsCRP levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale.

*Number=31 subjects

**Number= 56 subjects