

Table S1. Baseline characteristics of participants with and without CVDs in the Golestan Cohort Study						
	IHD or Stroke, N = 3371 (6.74)			Neither,	P	All,
	IHD, 3044 (90.30)	Stroke , 418 (12.40)	All, 3371	N = 46674 (93.26)		N = 50045
Age (years)					< 0.0001	
< 50	836 (27.46)	104 (24.88)	923 (27.38)	23692 (50.76)		24615 (49.19)
50–59	1085 (35.64)	163 (39.00)	1216 (36.07)	14357 (30.76)		15573 (31.12)
≥ 60	1123 (36.89)	151 (36.12)	1232 (36.55)	8625 (18.48)		9857 (19.70)
Gender					0.56	
Female	1787 (58.71)	217 (51.91)	1957 (58.05)	26854 (57.54)		28811(57.57)
Male	1257 (41.29)	201 (48.09)	1414 (41.95)	19820 (42.46)		21234 (42.43)
Place of residence					< 0.0001	
Urban	778 (25.56)	112 (26.79)	858 (25.45)	9176 (19.66)		10034 (20.05)
Rural	2266 (74.44)	306 (73.21)	2513 (74.55)	37498 (80.34)		40011 (79.95)
Education					< 0.0001	
Illiterate	2294 (75.36)	317 (75.84)	2540 (75.35)	32578 (69.80)		35118(70.17)
Literate	750 (24.64)	101 (24.16)	831 (24.65)	14096 (30.20)		14927 (29.83)
Marital status					< 0.0001	
Married	2510 (82.46)	345 (82.54)	2777 (82.38)	41178 (88.22)		43955 (87.83)
Unmarried	534 (17.54)	73 (17.46)	594 (17.62)	5496 (11.78)		6090 (12.17)
Ethnicity					< 0.0001	

Turkaman	2024 (66.49)	302 (72.25)	2269 (67.31)	34984 (74.95)	37253 (74.44)
Others	1020 (33.51)	116 (27.75)	1102 (32.69)	11690 (25.05)	12792 (25.56)
Smoking					< 0.0001
Current	275 (9.03)	49 (11.72)	317 (9.40)	5124 (10.98)	5441(10.87)
Former	367 (12.06)	48 (11.48)	400 (11.87)	2801 (6.00)	3201(6.40)
Non	2402 (78.91)	321 (76.79)	2654 (78.73)	38749 (83.02)	41403 (82.73)
History of Opium use	699 (22.96)	103 (24.64)	782 (23.20)	7718 (16.54)	< 0.0001 8500 (16.98)
History of alcohol use	178 (5.85)	17 (4.07)	190 (5.64)	1539 (3.30)	< 0.0001 1729 (3.45)
History of HTN	1509 (49.57)	228 (54.55)	1685 (49.99)	8192 (17.55)	< 0.0001 9877 (19.74)
History of DM	564 (18.53)	72 (17.22)	612 (18.15)	2832 (6.07)	< 0.0001 3444 (6.88)
BMI (kg/m²)					< 0.0001
< 18.5	131 (4.30)	20 (4.78)	149 (4.42)	2261(4.85)	2410 (4.82)
18.5–24.9	851 (27.97)	113 (27.03)	945 (28.04)	16984(36.42)	17929 (35.86)
25–29.9	1097 (36.05)	165 (39.47)	1222(36.26)	15715(33.70)	16937 (33.87)
≥ 30	964 (31.68)	120 (28.71)	1054 (31.28)	11671 (25.03)	12725 (25.45)
Physical activity					< 0.0001
Tertile 1	1477 (48.99)	249 (60.14)	1667 (49.94)	17043 (37.18)	18710 (38.05)
Tertile 2	1024 (33.96)	107 (25.85)	1103 (33.04)	16049 (35.02)	17152 (34.88)
Tertile 3	514 (17.05)	58 (14.01)	568 (17.02)	12742 (27.80)	13310 (27.07)
Wealth condition					0.002
Quintile 1	620 (20.37)	84 (20.10)	683 (20.26)	9222 (19.76)	9905 (19.79)

Quintile2	693 (22.77)	115 (27.51)	787 (23.35)	12373 (26.51)	13160 (26.30)
Quintile3	405 (13.30)	53 (12.68)	444 (13.17)	5740 (12.30)	6184 (12.36)
Quintile4	690 (22.67)	94 (22.49)	764 (22.66)	10297 (22.06)	11061 (22.10)
Quintile5	636 (20.89)	72 (17.22)	693 (20.56)	9042 (19.37)	9735 (19.45)

CVDs: Cardiovascular Diseases; IHD: Ischemic Heart Disease; HTN: Hypertension; DM: Diabetes Mellitus; BMI: Body Mass Index. Data are n (%).

Table S2. Characteristics of individuals with CVDs based on the number of main drugs* taken in the Golestan Cohort Study (n = 3371)

	0 drug	1drug	2 drugs	≥ 3 drugs	<i>p</i>	<i>P trend</i>
	N = 1451 (43.03)	N = 1043 (30.94)	N = 631 (18.72)	N = 246 (7.30)		
Age (years)					< 0.0001	< 0.0001
< 50	482 (52.22)	244 (26.44)	141 (15.28)	56 (6.07)		
50–59	493 (40.54)	388 (31.91)	243 (19.98)	92 (7.57)		
≥ 60	476 (38.64)	411 (33.36)	247 (20.05)	98 (7.95)		
Gender					< 0.0001	0.98
Female	811 (41.44)	674 (34.44)	349 (17.83)	123 (6.29)		
Male	640 (45.26)	369 (26.10)	282 (19.94)	123 (8.70)		
Place of residence					< 0.0001	< 0.0001
Urban	291 (33.92)	282 (32.87)	204 (23.78)	81 (9.44)		
Rural	1160 (46.16)	761 (30.28)	427 (16.99)	165(6.57)		

Education					< 0.0001	< 0.0001
Illiterate	1134 (44.65)	819 (32.24)	428 (16.85)	159 (6.26)		
literate	317 (38.15)	224 (26.96)	203 (24.43)	87 (10.47)		
Marital status					0.01	0.03
Unmarried	224 (37.71)	213 (35.86)	109 (18.35)	48 (8.08)		
Married	1227 (44.18)	830 (29.89)	522 (18.80)	198 (7.13)		
Ethnicity					0.53	0.62
Turkaman	963 (42.44)	719 (31.69)	426 (18.77)	161 (7.10)		
Others	488 (44.28)	324 (29.40)	205 (18.60)	85 (7.71)		
Duration of disease (years)					0.01	0.001
Quartile 1	395 (48.95)	213 (26.39)	141 (17.47)	58 (7.19)		
Quartile 2	345 (42.86)	262 (32.55)	147 (18.26)	51 (6.34)		
Quartile 3	329 (40.82)	260 (32.26)	158 (19.60)	59 (7.32)		
Quartile 4	316 (39.21)	271 (33.62)	153 (18.98)	66 (8.19)		
History of ever Smoking					0.11	0.11
Yes	333 (46.4)	205 (28.6)	122 (17.0)	57 (8.0)		
No	1118 (42.1)	838 (31.6)	509 (19.2)	189 (7.1)		
Current Smoking					0.002	< 0.0001
Yes	165 (52.05)	94 (29.65)	43 (13.56)	15 (4.73)		
No	1286 (42.11)	949 (31.07)	588 (19.25)	231 (7.56)		
History of Opiate use					0.27	0.67

Yes	350 (44.76)	220 (28.13)	155 (19.82)	57 (7.29)		
No	1101 (42.53)	823 (31.79)	476 (18.39)	189 (7.30)		
History of Alcohol use					0.60	0.92
Yes	84 (44.21)	54 (28.42)	34 (17.89)	18 (9.47)		
No	1367 (42.97)	989 (31.09)	597 (18.77)	228 (7.17)		
History of HTN					< 0.0001	< 0.0001
Yes	466 (27.66)	660 (39.17)	381 (22.61)	178 (10.56)		
No	985 (58.42)	383 (22.72)	250 (14.83)	68 (4.03)		
History of DM					< 0.0001	< 0.0001
Yes	188 (30.72)	215 (35.13)	119 (19.44)	90 (14.71)		
No	1263 (45.78)	828 (30.01)	512 (18.56)	156 (5.65)		
BMI (kg/m²)					< 0.0001	0.004
< 18.5	100 (67.11)	30 (20.13)	16 (10.74)	3 (2.01)		
18.5–24.9	485 (51.32)	260 (27.51)	152 (16.08)	48 (5.08)		
25–29.9	476 (38.95)	400 (32.65)	241 (19.72)	106 (8.67)		
≥ 30	390 (37.00)	353 (33.49)	222 (21.06)	89 (8.44)		
Physical activity					< 0.0001	< 0.0001
Tertile 1	673 (40.37)	509 (30.53)	336 (20.16)	149 (8.94)		
Tertile 2	352 (43.03)	280 (34.23)	137 (16.75)	49 (5.99)		
Tertile 3	418 (49.00)	240 (28.14)	150 (17.58)	45 (5.28)		
Wealth score					< 0.0001	< 0.0001

Quintile 1	337 (49.71)	218 (32.15)	92 (13.57)	31 (4.57)
Quintile 2	288 (50.09)	176 (30.61)	83 (14.43)	28 (4.87)
Quintile 3	381 (43.89)	265 (30.53)	163 (18.78)	59 (6.80)
Quintile 4	217(38.07)	184 (32.28)	121 (21.23)	48 (8.42)
Quintile 5	228 (33.53)	200 (29.41)	172 (25.29)	80 (11.76)
CVDs: Cardiovascular Diseases; HTN: Hypertension; DM: Diabetes Mellitus; BMI: Body Mass Index.* For drug counting, see Table 1.				

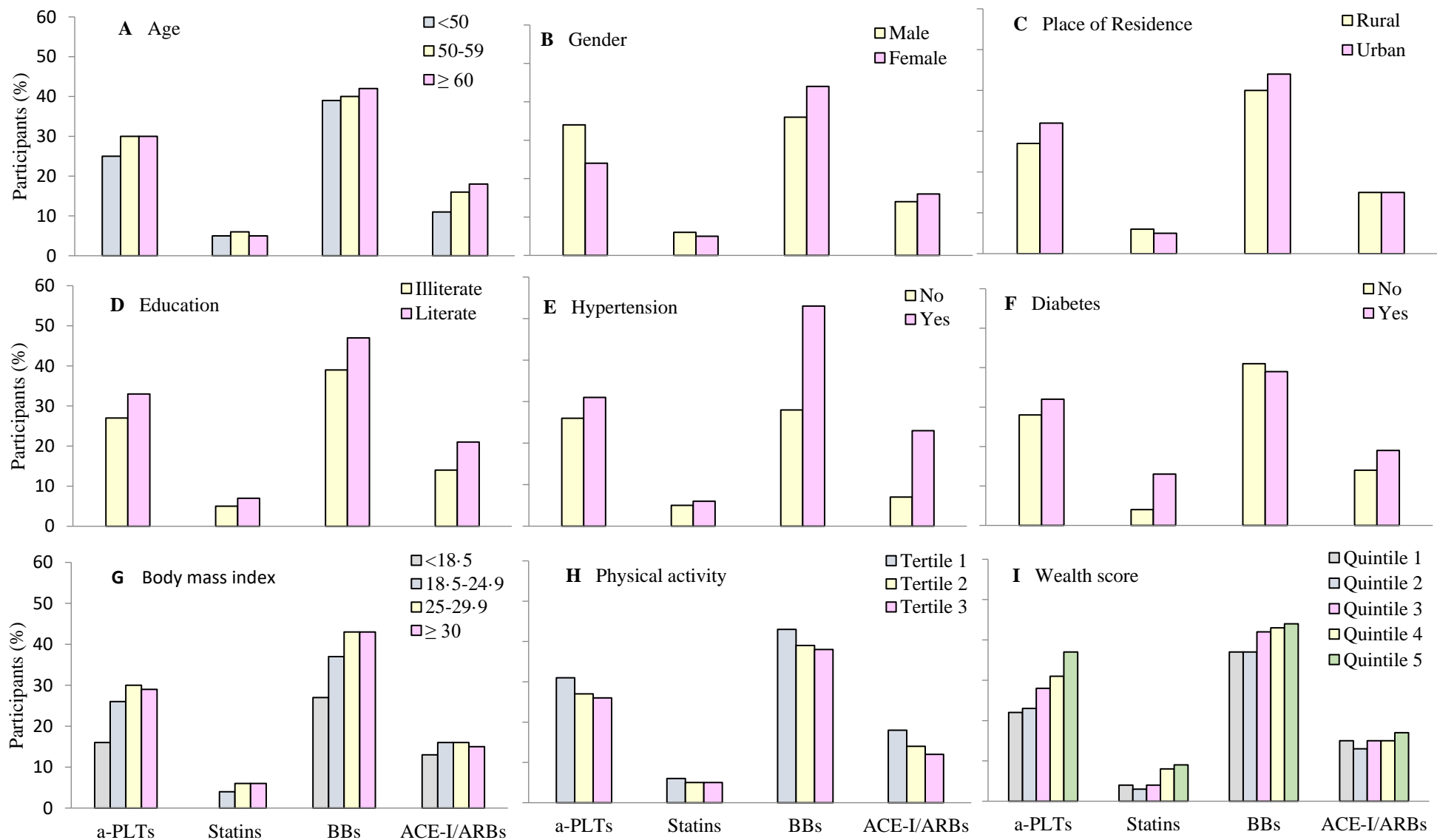
Table S3. Factors associated with ≥ 2 main drug* use in CVDs in the Golestan Cohort Study (n = 3371)						
	0–1 drug	≥ 2 Drug	Crude OR	AdjustedOR–1	AdjustedOR–2	Adjusted OR–3
	N = 2494 (73.98)	N = 877 (26.02)				
Age (years)				NA	NA	
< 50	726 (78.66)	197 (21.34)	1			1
50–59	881 (72.45)	335 (27.55)	1.40 (1.15–1.71)			1.32 (1.05–1.65)
≥ 60	887 (72.00)	345 (28.00)	1.43 (1.17–1.75)			1.40 (1.10–1.78)
Gender				NA	NA	
Male	1009 (71.36)	405 (28.64)	1			1
Female	1485 (75..88)	472 (24.12)	0.79 (0.68–0.92)			0.84 (0.67–1.05)
Place of residence						
Rural	1921 (76.44)	592 (23.56)	1	1	NA	1
Urban	573 (66.78)	285 (33.22)	1.61 (1.36–1.91)	1.59 (1.34–1.89)		1.23 (1.00–1.50)
Education						
Illiterate	1953 (76.89)	587 (23.11)	1	1	NA	1
Literate	541 (65.10)	290 (34.90)	1.78 (1.50–2.11)	2.03 (1.66–2.47)		1.59 (1.26–2.01)
Duration of disease						
Quartile 1	608 (75.34)	199 (24.66)	1	1	1	1
Quartile 2	607 (75.40)	198 (24.60)	1.00 (0.79–1.25)	0.98 (0.78–1.23)	0.94 (0.75–1.18)	0.87 (0.69–1.11)
Quartile 3	589 (73.08)	217 (26.92)	1.13 (0.90–1.41)	1.08 (0.86–1.35)	1.04 (0.83–1.31)	0.98 (0.77–1.24)

Quartile 4	587 (72.83)	219 (27.17)	1.14 (0.91–1.42)	1.08 (0.86–1.35)	1.01 (0.80–1.26)	0.88 (0.69–1.12)
Current Smoking						
No	2235 (73.18)	819 (26.82)	1	1	1	1
Yes	259 (81.70)	58 (18.30)	0.61 (0.45–0.82)	0.53 (0.39–0.72)	0.50 (0.36–0.68)	0.55 (0.39–0.78)
History of HTN						
No	1368 (81.14)	318 (18.86)	1	1	1	1
Yes	1126 (66.82)	559 (33.18)	2.13 (1.82–2.50)	2.25 (1.91–2.66)	2.36 (2.00–2.80)	2.15 (1.79–2.57)
History of DM						
No	2091 (75.79)	668 (24.21)	1	1	1	1
Yes	403 (65.85)	209 (34.15)	1.62 (1.34–1.96)	1.62 (1.34–1.95)	1.53 (1.26–1.85)	1.26 (1.03–1.55)
BMI (kg/m²)						
< 18.5	130 (87.25)	19 (12.75)	0.54 (0.33–0.90)	0.55 (0.33–0.92)	0.58 (0.35–0.97)	0.55 (0.30–0.99)
18.5–24.9	745 (78.84)	200 (21.16)	1	1	1	1
25–29.9	875 (71.60)	347 (28.40)	1.48 (1.21–1.80)	1.56 (1.27–1.91)	1.45 (1.18–1.78)	1.21 (0.97–1.51)
≥ 30	743 (70.49)	311 (29.51)	1.56 (1.27–1.91)	1.80 (1.45–2.23)	1.65 (1.32–2.06)	1.22 (0.97–1.55)
Physical activity						
Tertile 1	1182 (70.91)	485 (29.09)	1	1	1	1
Tertile 2	632 (77.26)	186 (22.74)	0.72 (0.59–0.87)	0.78 (0.63–0.97)	0.74 (0.59–0.91)	0.73 (0.58–0.92)
Tertile 3	658 (77.14)	195 (22.86)	0.72 (0.60–0.87)	0.81 (0.65–1.00)	0.73 (0.58–0.90)	0.76 (0.60–0.96)
Wealth score						
Quintile 1	555 (81.86)	123 (18.14)	1	1	1	1

Quintile 2	464 (80.70)	111 (19.30)	1.08 (0.81–1.43)	1.09 (0.82–1.45)	1.08 (0.81–1.43)	1.07 (0.79–1.46)
Quintile 3	646 (74.42)	222 (25.58)	1.55 (1.21–1.99)	1.60 (1.24–2.05)	1.54 (1.20–1.98)	1.49 (1.14–1.94)
Quintile 4	401 (70.35)	169 (29.65)	1.90 (1.46–2.48)	1.93 (1.48–2.52)	1.71 (1.30–2.25)	1.64 (1.22–2.19)
Quintile 5	428 (62.94)	252 (37.06)	2.66 (2.07–3.41)	2.67 (2.08–3.44)	2.17 (1.65–2.85)	2.14 (1.60–2.87)
<p>CVDs: Cardiovascular Diseases; HTN: Hypertension; DM: Diabetes Mellitus; BMI: Body Mass Index. OR–1: adjusted for age and gender; OR–2: adjusted for age, gender, place of residence, and education; OR–3: adjusted for all variables in the table. *For drug counting, see Table 1.</p>						

Table S4. Factors associated with use of specific drugs in CVDs in the Golestan Cohort Study (n = 3371)*				
	a-PLTs	Statins	ACE-I/ARBs	BBs
Age (years)				
≥ 60 vs. <50	1.29 (1.03–1.62)	0.97 (0.61–1.54)	1.85 (1.36–2.52)	1.14 (0.93–1.41)
Gender				
Female vs. Male	0.60 (0.48–0.74)	0.81 (0.53–1.25)	1.19 (0.90–1.57)	1.43 (1.17–1.76)
Place of residence				
Urban vs. Rural	1.32 (1.09–1.61)	0.90 (0.62–1.32)	1.01 (0.78–1.29)	1.21 (1.00–1.45)
Education				
Literate vs. Illiterate	1.34 (1.08–1.68)	1.32 (0.86–2.03)	1.72 (1.27–2.31)	1.46 (1.17–1.82)
Duration of disease				
Quartile 4 vs. 1	0.85 (0.68–1.08)	0.88 (0.58–1.35)	1.04 (0.78–1.38)	1.21 (0.98–1.51)
Active smoking				
Yes vs. No	0.68 (0.50–0.92)	0.51 (0.24–1.08)	0.83 (0.55–1.26)	0.71 (0.53–0.96)
History of HTN				
Yes vs. No	1.31 (1.10–1.55)	1.25 (0.89–1.75)	4.09 (3.21–5.21)	2.95 (2.52–3.46)
History of DM				

Yes vs. No	1.26 (1.03–1.54)	3.92 (2.83–5.43)	1.49 (1.18–1.89)	0.89 (0.72–1.07)
BMI				
<18.5 vs. NL	0.53 (0.31–0.92)	–	0.77 (0.41–1.44)	0.60 (0.38–0.94)
> 30 vs. NL	1.18 (0.94–1.48)	1.70 (1.03–2.78)	0.96 (0.72–1.28)	1.28 (1.04–1.58)
Physical activity				
Tertile 3 vs. 1	0.76 (0.61–0.95)	0.86 (0.56–1.33)	0.58 (0.43–0.78)	0.79 (0.65–0.97)
Wealth score				
Quintile 5 vs. 1	2.16 (1.63–2.86)	2.38 (1.34–4.21)	1.25 (0.89–1.76)	1.38 (1.06–1.79)
CVDs: Cardiovascular Diseases; HTN: Hypertension; DM: Diabetes Mellitus; BMI: Body Mass Index; a-PLTs: anti-Platelets; ACE-I/ARBs, Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers; BBs: beta-Blockers. *Adjusted for all variables in the table.				



Appendix Figure 1. Drug use in participants with ischemic heart disease or stroke based on main drug types. Classifications by **A)** age; **B)** gender; **C)** place of residence; **D)** education; **E)** hypertension; **F)** Diabetes mellitus; **G)** Body mass index; **H)** physical activity and **I)** wealth score were adjusted for all variables in the figure, current smoking, and duration of disease. a-PLTs: anti-Platelets; BBs: beta-Blockers; ACE-I/ARBs: Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers. For drug counting, see Table 1.