SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods. Incidence, relative survival, and prevalence.

Definitions:

λi represent the incidence rate at age i.

πi represent the prevalence at age i.

γi represent the relative mortality at age i (relative to the population)

and θi represent the mortality at age i.

Recursion relationships:

Let φi be the current mortality rate in those who do NOT have the prevalent condition.

Then $(1- \pi i) * \varphi i + \pi i * \varphi i * x = \theta i$, where x is the relative hazard of death for the condition relative to those without the condition. Therefore,

$\Gamma i = \varphi i * x / [(1- \pi i) * \varphi i + \pi i * \varphi i * x]$

Therefore,

$\varphi i * x = \gamma i * [(1- \pi i) * \varphi i + \pi i * \varphi i * x]$

$x * \varphi i * (1 - \gamma i * \pi i) = \gamma i * (1- \pi i) * \varphi i$

Thus,

$x = [\gamma i *(1- \pi i) * \varphi i] / [\varphi i * (1 - \gamma i * \pi i)]$

Now, for the recursion. We will actually not need "x", the relative hazard for those with and without the condition directly. In words, "The number with the disease at age i+1" = "number with disease at age i" - "number with disease who die" + "number of new cases"

The new population size is given by "population at i + 1" = "population at i" - "number of deaths". We arbitrarily allow death to occur first, and then we add incidence into the scheme. So, if we let Ni be the population size at the ith age, we have

$Ni+1 = Ni * (1 - \theta i)$

Number alive with disease at beginning of ith epoch: $\pi i * Ni$.

We now allow the force of differential mortality to occur. The number of prevalent cases who remain alive is:

$(\pi i * Ni) * (1 - \gamma i * \theta i)$

and the number of prevalent cases who die is:

$(\pi i * Ni) * \gamma i * \theta i$

The number of prevalent non-cases who die is the difference between the total number of deaths and this last expression. Thus, this number is:

$\theta i * Ni - (\pi i * Ni) * \gamma i * \theta i = Ni* \theta i * (1 - \pi i * \gamma i)$.

Note that this implies a constraint that $\gamma i < 1/ \pi i$.

The number of prevalent non-cases who remain alive is therefore:

$[N_i * (1- \pi_i) - N_i * \theta_i * (1 - \pi_i * \gamma_i)]$.

Let us now allow these prevalent non-cases to incur incidence, namely, we will have, at the end of the ith epoch:

$[N_i*(1- \pi_i) - N_i * \theta_i * (1 - \pi_i * \gamma_i)] * \lambda_i$

New prevalent cases, and total number of prevalent cases at the end of the epoch will therefore be:

$(\pi_i * N_i) * (1- \gamma_i * \theta_i) + [N_i*(1- \pi_i) - N_i * \theta_i * (1- \pi_i * \gamma_i)] * \lambda_i$

We already know the total number of individuals alive at the end of the epoch, namely $N_i * (1 - \theta_i)$. We can now calculate the prevalence at i + 1 as:

$\pi_{i+1} = [(\pi_i * N_i) * (1 - \gamma_i * \theta_i) + [N_i*(1- \pi_i) – N_i * \theta_i * (1 - \pi_i * \gamma_i)] * \lambda_i] \div [N_i * (1 - \theta_i)]$

We can eliminate N from this formula and this the recursion formula to get us from prevalence at age i to age i+1.

$\pi_{i+1} = [\pi_i * (1 - \gamma_i * \theta_i) + [(1- \pi_i) - \theta_i * (1 - \pi_i * \gamma_i)] * \lambda_i] \div [(1 - \theta_i)]$

How are the components of the above formula obtained?

λ_i: From the Poisson incidence model.

θ_i: We get this from standard life tables.

γ_i: We get this from a relative survival model, using our incidence cases, their age/sex/calendar year, and their death/follow-up times, and again the Minnesota White survival tables.

Specifically, we calculate $–\log(S0(t))$ for each incidence observation, and each follow-up/death time t. We then consider this transformed time to be proportional to the cumulative hazard with proportionality constant γ. We can then use a censored exponential model.

Table S1. Exclusion criteria based on the secondary causes. Individuals were excluded if any of the following were detected within a 1 year window around the index date.

Secondary Causes	Definition
Hypothyroidism	TSH >10 mIU/L
Significant Liver Disease	AST >130 IU/L, ALT >155 IU/L, ALP ≥200 IU/L, total bilirubin >2 mg/dL, significant alcohol abuse diagnosis codes, or AST/ALT ratio ≥2
Significant Kidney Disease	Creatinine ≥2.6 mg/dL, GFR <15 mL/min/BSA, urine protein/creatinine ratio ≥2.95 mg/mg, and 24-hours urine protein >3,000 mg/24h, nephrotic syndrome diagnosis codes, or renal failure diagnosis codes
Uncontrolled Diabetes	Hemoglobin A1c ≥9%
Morbid Obesity	BMI ≥35 kg/m^2
Pregnancy	Pregnancy, abortion, or delivery related diagnosis codes

ALP, Alkaline phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMI, Body Mass Index; BSA, Body Surface Area; GFR, Glomerular Filtration Rate; IU, International Unit; TSH, Thyroid Stimulating Hormone.

Table S2. ICD and CPT codes used for ascertainment of coronary heart disease.

Coronary Heart Disease	ICD-9	ICD-10	CPT
Angina	411.1, 413.0, 413.1, 413.9	I20.0, I20.8	
Myocardial infarction	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 429.71, 429.79, 412	I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.1, I25.2	
Chronic ischemic heart disease / Coronary atherosclerosis	414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.2, 414.3, 414.4, 414.8, 414.9	I25.10, I25.110, I25.111, I25.118, I25.119, I25.5, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9	
Percutaneous coronary revascularization	00.66, 36.03, 36.04, 36.06, 36.07, 36.09, V45.82	0270xxx, 0271xxx, 0272xxx, 0273xxx, 02C0xxx, 02C1xxx, 02C2xxx, 02C3xxx, 3E07017, 3E070PZ, 3E07317, 3E073PZ, Z95.5, Z98.61	92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996, 92973, 92974
Coronary artery bypass graft surgery	36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, V45.81	0210xxx, 0211xxx, 0212xxx, 0213xxx, Z95.1	33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536

Table S3. ICD and CPT codes used for ascertainment of cerebrovascular disease.

Cerebrovascular Disease	ICD-9	ICD-10	CPT
Stroke	434, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91 437.0, 437.1	I63.30, I63.311, I63.312, I63.313, I63.319, I63.321, I63.322, I63.323, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.39, I63.40, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.439, I63.441, I63.442, I63.443, I63.449, I63.49, I63.50, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.9, I67.2, I67.82, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9	
Transient ischemic attack	435.0, 435.1, 435.2, 435.3, 435.8, 435.9	G45.0, G45.1, G45.2, G45.8, G45.9	
Carotid artery disease	433, 433.00, 433.01, 433.10, 433.11, 433.20, 433.21, 433.30, 433.31, 433.80, 433.81, 433.90, 433.91	I63.00, I63.011, I63.012, I63.013, I63.019, I63.02, I63.031, I63.032, I63.033, I63.039, I63.09, I63.10, I63.111, I63.112, I63.113, I63.119, I63.131, I63.132, I63,133, I63.139, I63.19, I63.20, I63.211, I63.212, I63.213, I63.219, I63.22, I63.239, I63.29, I65.01, I65.02, I65.03, I65.09, I65.1, I65.21, I65.22, I65.23, I65.29, I65.8, I65.9	
Neuro-interventional procedures	00.61, 00.63, 38.11, 38.12, 39.28	037Hxxx, 037Jxxx, 037Kxxx, 037Lxxx, 037Mxxx, 037Nxxx, 03CGxxx, 03CHxxx, 03CJxxx, 03CKxxx, 03CLxxx, 03CMxxx, 03CNxxx, 03CPxxx, 03CQxxx	35301, 37215, 37216

Table S4. ICD codes used for ascertainment of peripheral artery disease.

Peripheral Artery Disease	ICD-9	ICD-10	CPT
Atherosclerotic peripheral artery disease	440.20, 440.21, 440.22, 440.23, 440.24, 440.29	I70.201, I70.202, I70.203, I70.209, I70.211, I70.212, I70.213, I70.219, I70.221, I70.222, I70.223, I70.229, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248, I70.249, I70.25, I70.261, I70.262, I70.263, I70.269, I70.291, I70.292, I70.293, I70.299	
Exclusion	237.70, 237.71, 237.72, 237.73, 237.79, 443.1, 446.0, 446.4, 446.5, 446.6, 446.7, 710.1, 747.10, 747.11, 747.22, 747.64	I73.1, M30.0, M31.1, M31.30, M31.31, M31.4, M31.5, M31.6, M34.0, M34.1, Q25.1, Q25.21, Q25.29, Q25.3, Q27.32, Q85.00, Q85.01, Q85.02, Q85.03, Q85.09	

Table S5. Incidence rate and prevalence of isolated hypertriglyceridemia.

	Incidence Rate* (95% CI)		Prevalence† (95% CI)	
	Olmsted County	US‡	Olmsted County	US‡
Isolated Hypertriglyceridemia (triglyceride ≥500 mg/dL and Non-HDL-C <190 mg/dL)				
Male (n = 843)	68.44 (63.90-73.22)	75.49 (70.28-80.70)	2.02% (1.86-2.16)	2.26% (2.08-2.42)
Female (n = 383)	28.65 (25.85-31.67)	30.95 (27.80-34.09)	0.89% (0.79-1.00)	1.03% (0.91-1.15)
Total (n = 1,226)	47.73 (45.09-50.48)	52.86 (49.85-55.87)	1.42% (1.33-1.51)	1.61% (1.50-1.71)

* Incidence rates for 100,000 person-year. Incidence rates were measured by 1,231,727 person-year of follow-up in males and 1,336,917 in females.
† Prevalence rates are calculated as the mean value of adults (18-95 years), weighted to the population counts of Olmsted County or the United States whites from 2010 census estimates. Confidence limits are calculated using the 2.5th and 97.5th percentile of all prevalence rates across 1,000 bootstrapped samples (within each sample, the prevalence rate is the mean rate across all ages, as above).
‡ Sex-specific incidence rates are adjusted to the age distribution of the US white population from 2010, overall incidence rates are adjusted to the age and sex distribution of the US white population from 2010.

Table S6. Lipid-lowering medications in the 18-month period before the index date, after the index date, and before the last follow-up, based on the indication of treatment and age categories.

	No Treatment	Non-statin only	Statin only	Both statin and non-statin
All cases (all ages) (n=517)				
18-months before the index date	72%	7%	17%	5%
18-months after the index date	48%	21%	18%	13%
18-months before the last follow-up*	32%	14%	38%	17%
Primary prevention† (all ages) (n=412)				
18-months before the index date	78%	7%	12%	3%
18-months after the index date	54%	22%	14%	10%
18-months before the last follow-up*	35%	16%	35%	15%
Secondary prevention‡ (all ages) (n=105)				
18-months before the index date	49%	4%	35%	12%
18-months after the index date	27%	15%	30%	28%
18-months before the last follow-up*	18%	7%	49%	26%
Primary prevention† (<40 years) (n=130)				
18-months before the index date	86%	9%	5%	0%
18-months after the index date	65%	23%	6%	6%
18-months before the last follow-up*	53%	22%	18%	7%
Primary prevention† (40 - 54 years) (n=178)				
18-months before the index date	80%	6%	11%	3%
18-months after the index date	54%	25%	13%	7%
18-months before the last follow-up*	31%	14%	37%	18%
Primary prevention† (55 – 69 years) (n=84)				
18-months before the index date	68%	7%	23%	2%
18-months after the index date	39%	18%	26%	17%
18-months before the last follow-up*	18%	10%	54%	18%
Primary prevention† (≥70 years) (n=20)				
18-months before the index date	50%	5%	25%	20%
18-months after the index date	35%	15%	25%	25%
18-months before the last follow-up*	32%	21%	37%	11%

* In cases with at least 36 months follow-up. †Primary prevention is defined as cases with no coronary heart disease, cerebrovascular disease, or peripheral artery disease at the time of prescription. ‡Secondary prevention is defined as cases with coronary heart disease, or cerebrovascular disease, or peripheral artery at the time of prescription.

Table S7. Rate of baseline and incident event in cases and controls.

	Controls (n = 766)	**Cases (n = 517)**	***P*-value***
CHD events	155 (20.2%)	166 (32.1%)	
Baseline CHD events	73 (9.5%)	84 (16.2%)	<0.001
New CHD events†	82 (11.8%)	82 (18.9%)	<0.001
CVD events	78 (10.2%)	77 (14.9%)	
Baseline CVD events	22 (2.9%)	32 (6.2%)	0.005
New CVD events†	56 (7.5%)	45 (9.3%)	0.139
PAD events	19 (2.5%)	19 (3.7%)	
Baseline PAD events	9 (1.2%)	9 (1.7%)	0.401
New PAD events†	10 (1.3%)	10 (2.0%)	0.305
Composite Endpoint	198 (25.8%)	195 (37.7%)	
Baseline composite events	89 (11.6%)	105 (20.3%)	<0.001
New composite events†	109 (16.1%)	90 (21.8%)	0.003

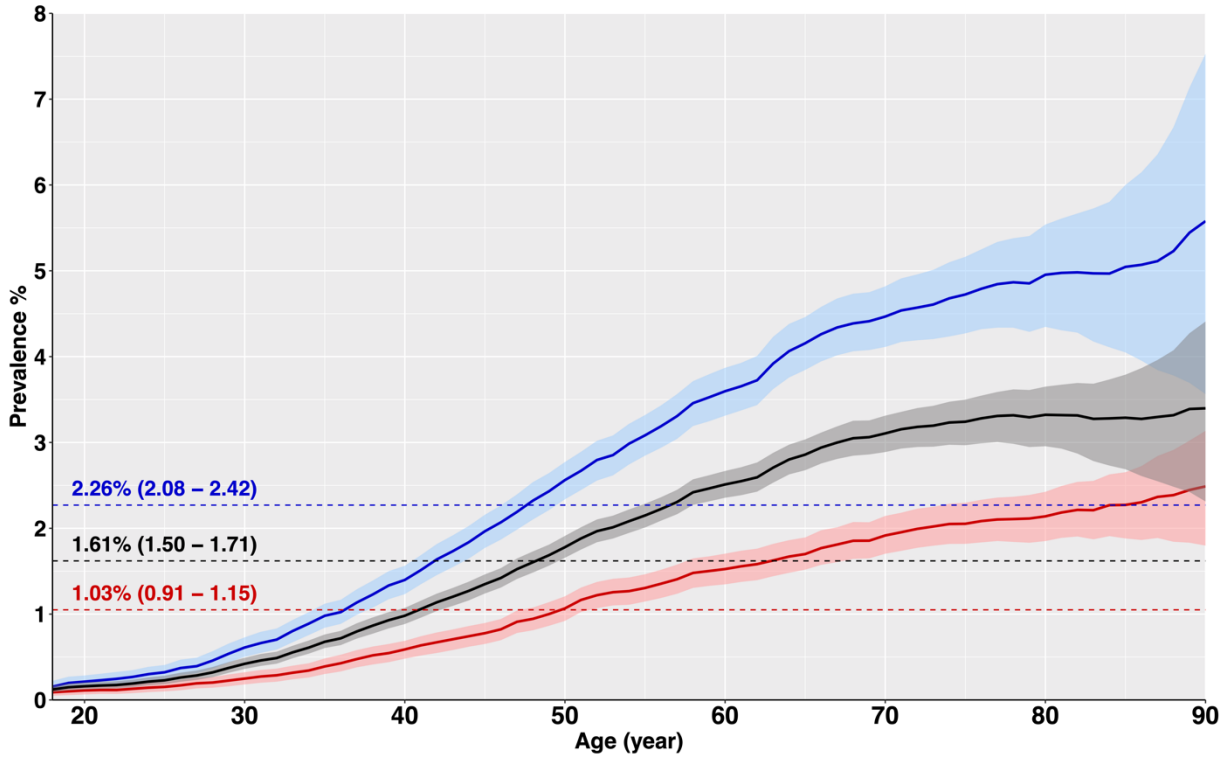
CHD, coronary heart disease; CVD, cerebrovascular disease; PAD; peripheral artery disease. *P-values are unadjusted logistic (baseline) and Cox (new) event models. †Excludes people with baseline events.

Table S8. Hazard ratios for CHD, CVD, PAD, and composite endpoint in Cox proportional hazards regression model in PIH cases in comparison with controls.

	CHD (number of events = 164)		CVD (number of events = 101)		PAD (number of events = 20)		Composite Endpoint (number of events = 199)	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Primary Isolated Hypertriglyceridemia	1.53 (1.06 - 2.20)	0.022	1.06 (0.65 - 1.73)	0.813	1.27 (0.43 - 3.75)	0.668	1.28 (0.92 - 1.80)	0.148
Age (per 10 year increase)	1.75 (1.53 – 2.00)	<0.001	1.94 (1.62 - 2.32)	<0.001	1.53 (1.04 - 2.24)	0.029	1.84 (1.62 - 2.08)	<0.001
Sex (male vs female)	1.82 (1.25 - 2.66)	0.002	1.47 (0.92 - 2.35)	0.112	2.26 (0.71 - 7.22)	0.168	2.04 (1.44 - 2.90)	<0.001
Race (non-white vs white)	1.05 (0.57 - 1.94)	0.881	0.69 (0.27 - 1.74)	0.426	0.56 (0.07 - 4.50)	0.588	1.11 (0.64 - 1.93)	0.715
Education		0.023		0.362		0.712		0.041
12 – 15 years	3.10 (1.22 – 7.87)		0.83 (0.40 - 1.74)		0.63 (0.12 – 3.28)		1.99 (0.97 - 4.06)	
≥ 16 years	2.34 (0.90 - 6.04)		0.64 (0.30 – 1.38)		0.91 (0.18 – 4.68)		1.47 (0.71 - 3.04)	
Family history of CHD	2.45 (1.61 - 3.72)	<0.001	1.39 (0.75 - 2.56)	0.299	1.01 (0.23 - 4.42)	0.990	1.93 (1.29 - 2.89)	0.001
Hypertension	1.02 (0.71 - 1.45)	0.932	1.96 (1.18 - 3.27)	0.010	1.32 (0.45 - 3.88)	0.614	1.06 (0.77 - 1.47)	0.710
Diabetes Mellitus	1.21 (0.80 - 1.81)	0.364	1.29 (0.78 - 2.15)	0.325	1.68 (0.54 - 5.24)	0.370	1.24 (0.84 - 1.82)	0.283
Smoking status		0.079		0.545		0.751		0.069
Missing	1.24 (0.65 - 2.37)		1.27 (0.58 – 2.79)		1.83 (0.38 – 8.78)		1.48 (0.86 - 2.55)	
Tobacco history	1.54 (1.06 - 2.25)		1.30 (0.81 - 2.06)		1.21 (0.42 - 3.49)		1.47 (1.05 - 2.06)	
Body Mass Index		0.810		0.284		0.980		0.416
Underweight, <18.5 kg/m^2	1.72 (0.23 - 13.03)		NA		NA		1.02 (0.14 - 7.59)	
Missing	1.16 (0.43 - 3.14)		0.24 (0.05 - 1.14)		0.71 (0.06 – 9.12)		0.62 (0.25 - 1.58)	
Overweight, 25-29 kg/m^2	1.29 (0.80 - 2.08)		0.69 (0.39 - 1.22)		0.65 (0.18 - 2.36)		0.86 (0.57 - 1.29)	
Obese, 30-34 kg/m^2	1.36 (0.80 - 2.31)		0.90 (0.49 - 1.68)		0.73 (0.17 - 3.08)		1.13 (0.72 - 1.77)	
Total Cholesterol		0.787		0.988		0.897		0.869
200-239 mg/dL	0.92 (0.66 - 1.28)		0.97 (0.63 - 1.48)		1.26 (0.48 - 3.27)		1.05 (0.77 - 1.41)	
≥240 mg/dL	1.22 (0.44 – 3.39)		0.97 (0.23 - 4.08)		NA		1.25 (0.50 - 3.13)	

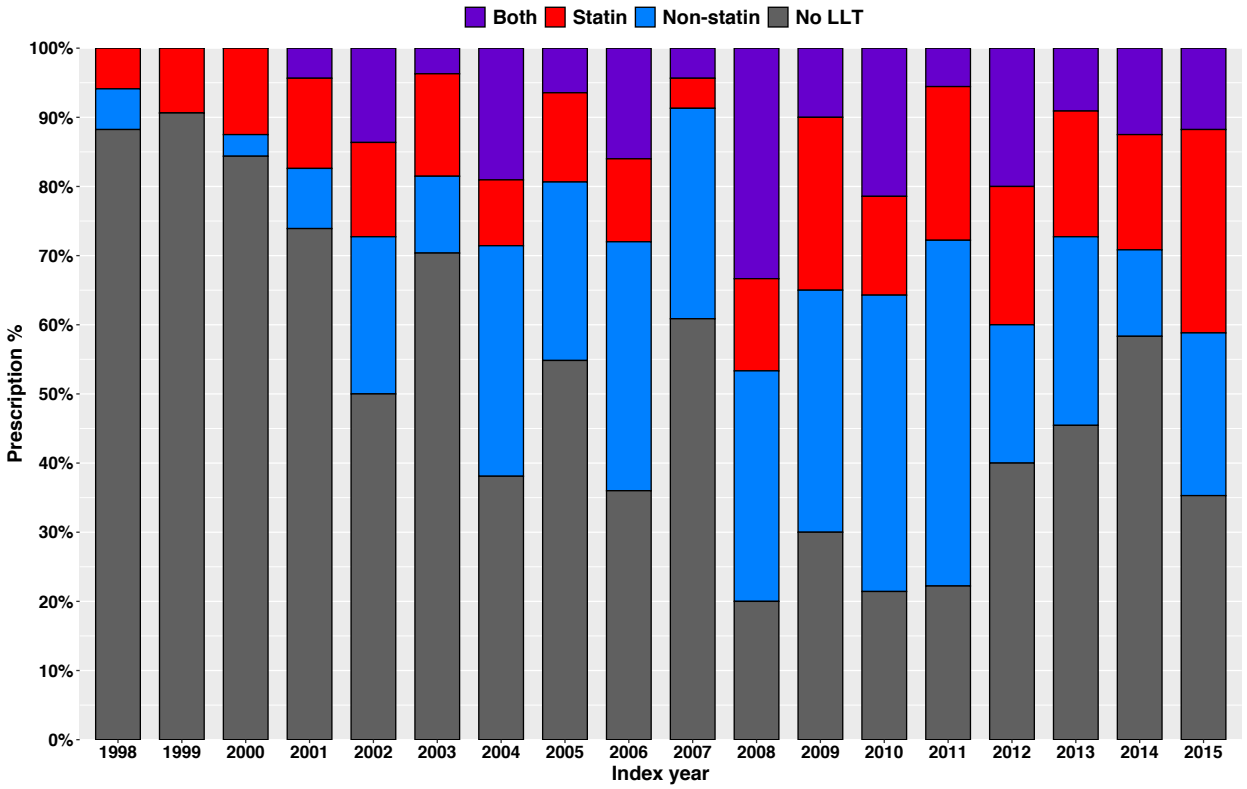
CHD, coronary heart disease; CVD, cerebrovascular disease; PAD; peripheral artery disease.

Figure S1. Age-specific prevalence (%) of isolated hypertriglyceridemia in adults (triglyceride ≥500 mg/dL and Non-HDL-C <190 mg/dL) adjusted to the US white population.



Males are depicted in blue and females in red and the overall in black. Dashed lines represent mean prevalence values for adults (age 18-95 years).

Figure S2. Prescription of lipid-lowering medication for primary prevention in the 18-month period after detection of primary isolated hypertriglyceridemia.



LLT, lipid-lowering treatment.

Figure S3. Status of control based on three thresholds in primary vs. secondary prevention and in differentage categories.