SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics and distribution of risk enhancers, statified by study cohort and risk categories.

	ARIC (n=12,906)			CHS (n=3,626)			MESA (n=6,410)		
	<7.5%	7.5 to <20%	≥20%	<7.5%	7.5 to <20%	≥20%	<7.5%	7.5 to <20%	≥20%
No. (%) by cohort	9209 (71.4)	3016 (23.4)	681 (5.3)	470 (13)	1860 (51.3)	1296 (35.7)	4220 (65.8)	1749 (27.3)	441 (6.9)
Baseline characteristics									
Age, mean (SD), years	52.8 (5.4)	57.1 (5.4)	57.7 (5.3)	67.2 (2.1)	70.1 (3.5)	73.1 (4.1)	58.1 (8.7)	66.9 (7.9)	70.5 (7.9)
Female, %	65.5	30.8	26.8	92.1	65	45.7	60.4	39.9	29.2
White, %	77.2	73.3	64.7	91.4	94.6	96.3	32.8	46.4	59.1
African American, %	22.8	26.7	35.2	6.0	5.1	3.6	24.6	34.6	34.7
Total Cholesterol, mean (SD), mg/dL	208 (38.2)	226 (43.4)	234 (50.2)	207 (34.5)	213 (37)	215 (41.7)	192 (33.8)	195 (36.1)	199 (37.9)
HDL-C, mean (SD), mg/dL	56.0 (17.3)	43.8 (12.1)	40.9 (11.3)	66.9 (17.0)	55.9 (15.1)	50.2 (13.4)	52.8 (15.1)	48.1 (13.4)	46.3 (13.1)
LDL-C, mean (SD), mg/dl	130 (35.8)	152 (40.2)	158 (46.1)	121 (32.4)	134 (33.9)	138 (37.7)	115 (30.6)	120 (32.6)	124 (33.9)
Untreated SBP, mean(SD), mmHg	114 (14)	128 (18)	146 (26)	116 (14)	130 (17)	145 (20)	116 (16)	132 (19)	147 (19)
Treated SBP, mean (SD), mmHg	122 (14)	133 (17)	147 (22)	116 (15)	130 (16)	149 (20)	125 (17)	138 (20)	153 (22)
BP meds, %	14.1	35.4	58.8	16.3	34.1	54.4	26.8	52.1	65.1
Current smoker, %	17.4	44.2	60.5	5.7	12.2	16.6	9.3	19.8	25.1
Diabetes, %	2.6	15.2	52.8	1.2	6.5	45.2	4.5	20.1	38.1
Statin use, %	0.40	0.56	0.44	4.8	1.1	0.54	16.4	12.9	4.1
Risk enhancers									
Triglyceride≥175 mg/dL, %	11.7	28.8	44.0	10.0	18.8	28.9	17.4	23.3	26.3

LDL-C≥160 mg/dL, %	19.6	40.0	44.7	11.2	22.8	26.7	8.1	11.1	13.1
Non-HDL-C≥190 mg/dL, %	16.8	40.6	49.9	7.2	18.4	23.9	7.5	11.4	14.2
Metabolic syndrome, %	17.4	44.8	69.4	7.7	25.8	48.7	19.9	39.8	52.5
CKD, %	0.46	1.9	4.2	28.4	31.6	44.2	7.6	16.8	23.3
ABI≤0.9, %	3.0	4.7	10.3	2.3	5.7	14.4	1.5	6.1	9.8
hsCRP≥2 mg/dL, %	N/A	N/A	N/A	46.9	54.5	64.3	45.9	52.8	55.6
Lp(a)≥50 mg/dL, %	N/A	N/A	N/A	45.7	45.5	42.9	18.0	20.6	21.6
ApoB≥130 mg/dL, %	6.4	18.6	25.7	N/A	N/A	N/A	17.1	23.9	23.9
Family history of premature CVD, %	8.2	8.0	8.5	N/A	N/A	N/A	26.7	29.2	23.6
CAC>0 Agatston unit, %	N/A	N/A	N/A	N/A	N/A	N/A	37.7	65.8	78.6

PCE, pooled cohort equation; No., number; SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; CKD, chronic kidney disease; Lp(a), lipoprotein (a); ApoB, apolipoprotein B; CVD, cardiovascular disease; CAC, coronary artery calcium

Table S2. Incremental utility of CAC score over the pooled cohort equation across categories of risk enhancer (as defined by the optimum cutpoint of ≥3 risk enhancers).

No of risk enhancers	PCE alone	PCE+cac	P value for improvement	IDI (p value)	NRI across 7.5%-20% cutpoints	Category-free NRI (p value)
<3 risk enhancers	0.757	0.770	0.01	0.006 (<0.001)	0.04 (0.05)	0.577 (<0.001)
>=3 risk enhancers	0.812	0.825	0.10	0.009 (0.12)	-0.028 (0.62)	0.535 (<0.001)

Table S3. Evaluation of risk enhancers in continuous form*

	Strength of association		C-statistic			Integrated discrimination	Net reclassification	
	HR per SD	P value	PCE alone	PCE+risk enhancer	P value for improvement	IDI (p value)	NRI across 7.5%-20% cut-points (p value)	Category-free NRI (p value)
Triglyceride	1.03 (0.98, 1.08)	0.25	0.789	0.789	0.71	-0.0001 (0.89)	0.0003 (0.99)	0.013 (0.19)
LDL-C	1.00 (0.84, 1.12)	0.87	0.789	0.789	0.43	-0.0002 (0.54)	0.003 (0.18)	0.019 (0.20)
GFR	0.85 (0.80, 0.91)	<0.001	0.789	0.790	0.23	0.0009 (0.79)	0.001 (0.82)	0.051 (0.26)
ABI	0.84 (0.81, 0.87)	<0.001	0.789	0.792	0.01	0.004 (0.02))	0.018 (0.01)	-0.004 (0.78)
hsCRP (ln)†	1.09 (1.02, 1.16)	0.01	0.796	0.796	0.97	0.001 (0.04)	-0.01 (0.31)	0.103 (0.004)
Lp(a) (ln) †	1.07 (0.99, 1.16)	0.06	0.796	0.798	0.04	0.003 (0.02)	0.02 (0.06)	0.124 (<0.001)
ApoB	1.06 (0.96, 1.16)	0.06	0.773	0.775	0.03	0.001 (0.51)	0.019 (0.02)	0.124 (<0.001)
Aggregate risk enhancer†	1.21 (1.08-1.37)††	0.001	0.762	0.763	0.40	0.010 (0.004)	0.043 (0.03)	0.127 (0.01)
CAC (ln+1)†β	1.56 (1.37, 1.77)	<0.001	0.7613	0.7822	0.001	0.012 (0.002)	0.096 (<0.001)	0.464 (<0.001)

HR, hazard ratio; SD, standard deviation; LDL-C, low density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; ApoB, Apolipoprotein B; GFR, glomerular filtration rate; Lp(a), lipoprotein (a); ABI, ankle brachial index; CAC, coronary artery calcium; PCE; pooled cohort equation IDI, integrated discrimination index; NRI, net reclassification index

* Model calibration was optimum (p≥0.35) across all model (not shown in the table). Non-HDL was not assessed due to collinearity with total cholesterol and HDL in the multivariable model

†hsCRP, Lp(a) and CAC score have skewed distribution. Hence, natural logarithm was used to normalize their distribution prior to analysis

††Hazard ratio represents for each additional significant risk enhancer

β There was weak correlation between the CAC score and the number of enhancers (correlation coefficient (r) = 0.20, p<0.001). Among all the 6 risk enhancers included in the aggregate score, GFR (r = -0.21, p<0.001) was the most strongly correlated with CAC value

Table S4. Reclassification by aggregate risk enhancer score (in continuous form).

PCE alone	PCE with combined risk enhancer				Risk reclassification	
	<7.5%	7.5 to <20%	≥20%	Row total	Higher, No. (%)	Lower, No. (%)
Events (n=305)						
<7.5%	149	16		165	16 (9.7)	NA
7.5 to <20%	11	102	8	121	8 (6.6)	11 (9.1)
≥20%		1	18	19	NA	1 (5.3)
Column total	160	119	26	305	24 (7.9)	12 (3.9)
Nonevent (n=6,105)						
<7.5%	4,970	118		5,088	118 (2.3)	NA
7.5 to <20%	139	762	22	923	22 (2.4)	139 (15.1)
≥20%		22	72	94	NA	22 (23.4)
Column total	5,109	902	94	6,105	140 (2.3)	161 (2.6)
Net reclassification improvement						
Overall					4.3%	(p=0.03)
Intermediate group (7.5 to <20%)					10.2%	

PCE, pooled cohort equation; No., number; NA, not applicable

Table S5. Strength of association between 2018 guideline-recommended risk enhancers after adjusting for the pooled cohort equation (analysis restricted to the ARIC cohort).

Risk enhancer	HR(95% CI)	P value
Triglyceride≥175	0.90 (0.76, 1.07)	0.25
LDL-C≥160	1.19 (0.96, 1.46)	0.10
Non-HDL≥190	1.29 (1.01, 1.60)	0.04
Metabolic syndrome	0.93 (0.79, 1.09)	0.41
HsCRP≥2	N/A	
ApoB≥130	1.11 (0.98, 1.37)	0.08
CKD	2.06 (1.43, 2.96)	<0.001
Family history of premature CVD	1.21 (1.00, 1.53)	0.05
Lp(a)≥50	N/A	
ABI≤0.9	1.63 (1.26, 2.12)	<0.001

HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; ApoB, Apolipoprotein B; CKD, chronic kidney disease; Lp(a), lipoprotein (a); ABI, ankle brachial index; CVD, cardiovascular disease; CAC, coronary artery calcium; ARIC, Atherosclerosis Risk in Communities Study

Table S6. Incremental utility of risk enhancers and CAC score over the pooled cohort equation (analysis restricted to ARIC cohort).

	C-statistic			Integrated discrimination	Net reclassification
	PCE alone	PCE+risk enhancer	P value for improvement	IDI (p value)	NRI across 7.5%-20% cutpoints
Triglyceride≥175 mg/dL	0.779	0.779	0.33	-0.0001 (0.95)	-0.004 (0.36)
LDL-C≥160 mg/dL	0.779	0.779	0.43	0.0003 (0.22)	-0.002 (0.80)
Non-HDL-C≥190 mg/dL	0.779	0.780	0.08	0.0005 (0.22)	-0.003 (0.66)
Metabolic syndrome	0.779	0.780	0.58	-0.0001 (0.14)	0.002 (0.52)
CKD	0.779	0.780	0.16	0.002 (0.02)	-0.002 (0.78)
ABI≤0.9	0.779	0.781	0.16	0.002 (0.01)	0.008 (0.25)
hsCRP≥2 mg/dL	N/A				
Lp(a)≥50 mg/dL	N/A				
ApoB≥130 mg/dL	0.779	0.779	0.89	0.0002 (0.87)	-0.002 (0.58)
Family history of premature CVD	0.779	0.779	0.59	0.0002 (0.31)	0.004 (0.51)

HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; ApoB, Apolipoprotein B; CKD, chronic kidney disease; Lp(a), lipoprotein (a); ABI, ankle brachial index; CVD, cardiovascular disease; CAC, coronary artery calcium; PCE; pooled cohort equation IDI, integrated discrimination index; NRI, net reclassification index

Figure S1. Sample selection.
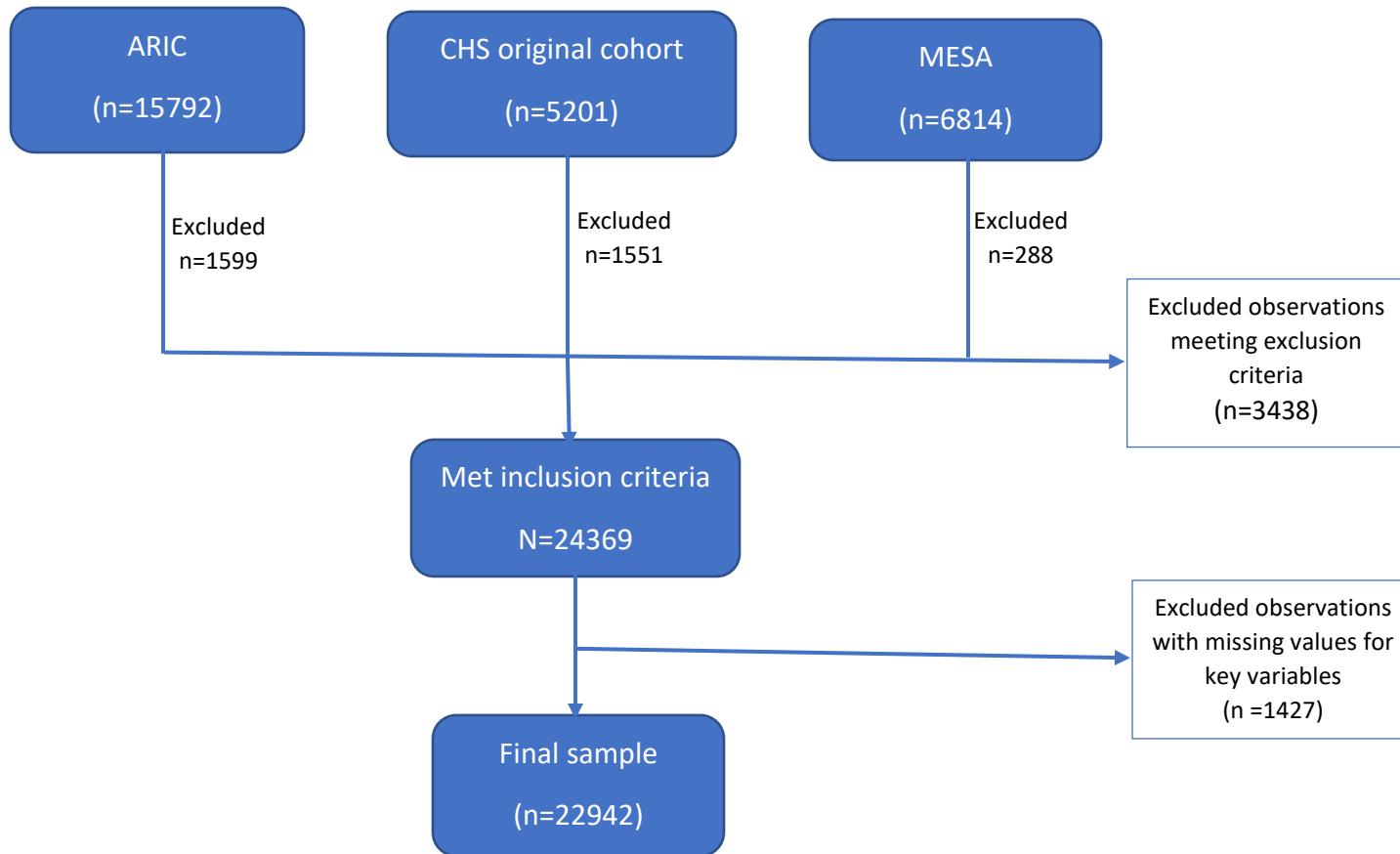
Key variables included variables required for calculation of the pooled cohort equation -- age, sex, race, treated or untreated systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), current smoking, diabetes—and statin use.

Figure S2. Distribution of the number of risk enhancers among participants in the Multi-Ethnic Study of Atherosclerosis (MESA).
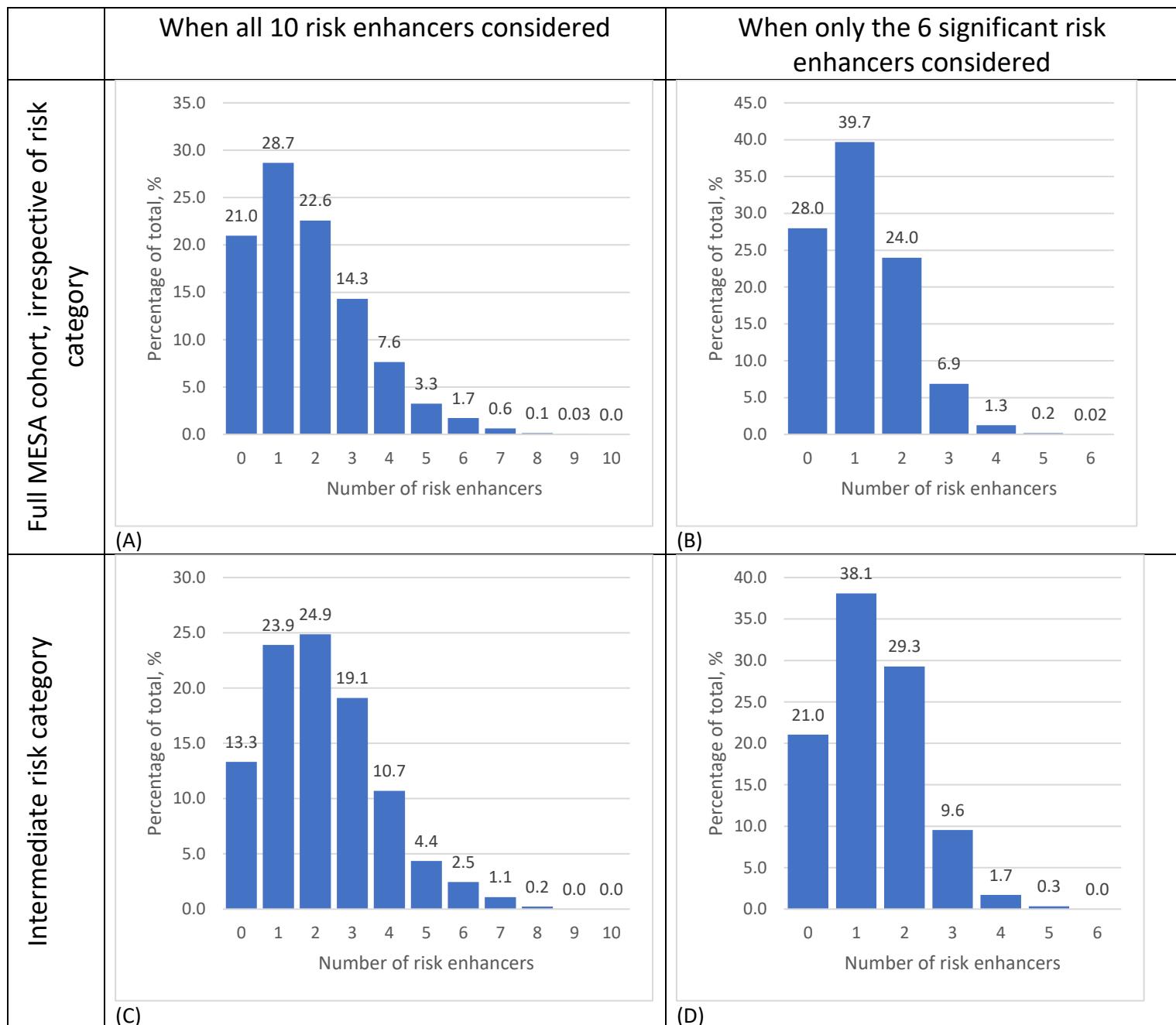
Figure S3. Rate of incident ASCVD by number of significant risk enhancers (hsCRP ≥2 mg/L, ApoB ≥130 mg/dL , CKD, family history of premature CVD, Lp(a) ≥50 mg/dL, and ABI<0.9): (A) irrespective of risk category, (B) Among participants with intermediate risk.
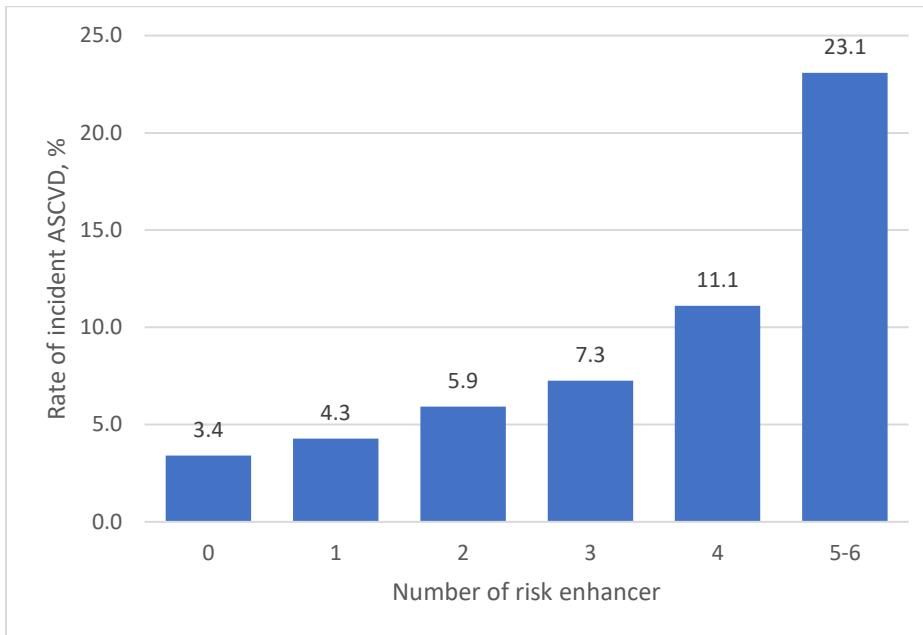
(A)
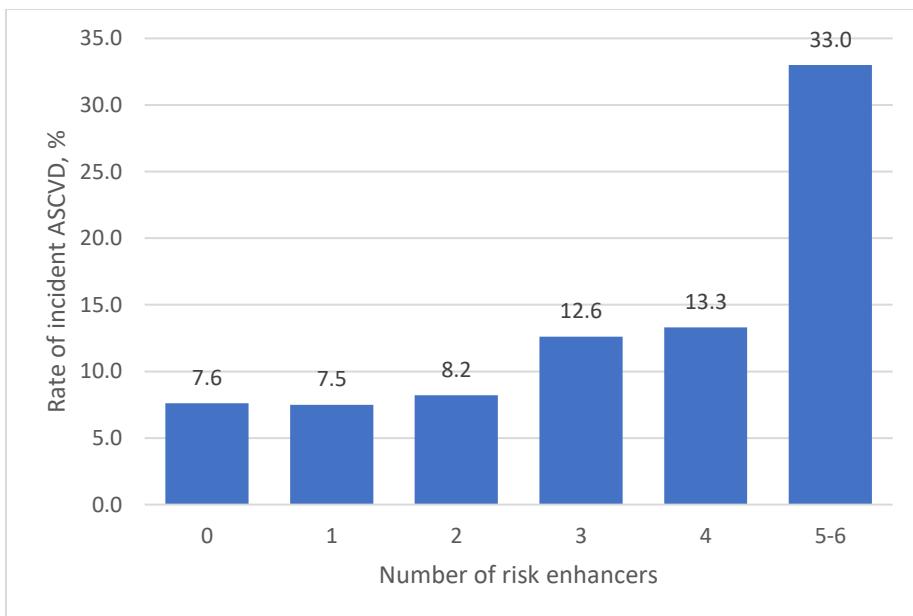
(B)

The group of 5 and 6 risk enhancers was combined due to very few participants with 6 risk enhancers