

Table e-1		
	HR (95% CI)	p-value
HPFS		
Caffeine		
1	1.00 (reference)	
2	0.90 (0.71, 1.14)	0.37
3	0.79 (0.61, 1.01)	0.06
4	0.69 (0.53, 0.89)	<0.01
5	0.54 (0.39, 0.73)	<0.0001
Smoking		
1	1.00 (reference)	
2	0.82 (0.61, 1.11)	0.20
3	0.82 (0.63, 1.07)	0.14
4	0.70 (0.56, 0.88)	<0.01
5	0.47 (0.30, 0.73)	<0.001
Physical activity		
1	1.00 (reference)	
2	0.78 (0.60, 1.02)	0.07
3	0.72 (0.55, 0.94)	0.02
4	0.80 (0.61, 1.03)	0.09
5	0.64 (0.48, 0.84)	<0.01
Family history		
Present	1.00 (reference)	
Absent	0.44 (0.32, 0.61)	<0.0001
Flavonoid		
1	1.00 (reference)	
2	0.84 (0.64, 1.11)	0.22
3	0.85 (0.65, 1.12)	0.25
4	0.99 (0.76, 1.29)	0.94
5	0.82 (0.62, 1.09)	0.18
Dietary urate index		
1	1.00 (reference)	
2	0.99 (0.78, 1.27)	0.95
3	0.91 (0.71, 1.17)	0.47
4	0.91 (0.70, 1.17)	0.45
5	0.75 (0.57, 0.99)	0.05
NHS		
Caffeine		
1	1.00 (reference)	
2	0.90 (0.70, 1.15)	0.40
3	0.84 (0.65, 1.09)	0.20

	4	0.76 (0.58, 1.00)	0.05
	5	1.04 (0.79, 1.38)	0.76
Smoking			
	1	1.00 (reference)	
	2	0.82 (0.64, 1.04)	0.10
	3	0.65 (0.47, 0.89)	<0.01
	4	0.62 (0.48, 0.79)	<0.001
	5	0.27 (0.16, 0.46)	<0.0001
Physical activity			
	1	1.00 (reference)	
	2	1.13 (0.84, 1.50)	0.42
	3	1.02 (0.76, 1.36)	0.92
	4	1.00 (0.75, 1.34)	0.98
	5	0.89 (0.66, 1.20)	0.44
Family history			
	Present	1.00 (reference)	
	Absent	0.48 (0.36, 0.64)	<0.0001

Table e-2a: Tests of interactions on the multiplicative and additive scale for the HPFS

HPFS			
Predictor 1	Predictor 2	HR (95% CI)	p-value
Caffeine	Smoking		
Low	Never	1.00 (reference)	
High	Never	0.74 (0.58, 0.93)	0.01
Low	Ever	0.77 (0.62, 0.96)	0.02
High	Ever	0.48 (0.38, 0.61)	<0.0001
		Additive interaction:	
		RERI	-0.25 (95% CI:-0.78, 0.28)
		AP (95% CI)	-0.13 (-0.41, 0.14)
		P_{AP} for interaction	0.35
		Synergy Index	0.79 (0.50, 1.24)
		Multiplicative interaction:	
		Caffeine (high/low) * smoking (never/ever)	0.84 (0.64, 1.09) $P_{multi} = 0.18$
		Caffeine (100 mg/day) * smoking categories	$P_{multi} = 0.68$
Caffeine	Physical Activity		
Low	Low	1.00 (reference)	
High	Low	0.73 (0.57, 0.93)	0.01
Low	High	0.92 (0.74, 1.15)	0.46
High	High	0.62 (0.48, 0.81)	<0.001
		Additive interaction:	
		RERI	-0.03 (-0.52, 0.46)
		AP (95% CI)	-0.02 (-0.27, 0.23)
		P_{AP} for interaction	0.90
		Synergy Index	0.97 (0.55, 1.69)
		Multiplicative interaction:	
		Caffeine (high/low) * physical activity (high/low)	0.93 (0.66, 1.32) $P_{multi} = 0.69$
		Caffeine (100 mg/day) * physical activity (quintiles)	$P_{multi} = 0.77$
Caffeine	Family History		
Low	Yes	1.00 (reference)	
High	Yes	0.53 (0.27, 1.02)	0.06
Low	No	0.37 (0.25, 0.55)	<0.0001
High	No	0.26 (0.18, 0.40)	<0.0001
		Additive interaction:	
		RERI	1.46 (-0.27, 3.18)
		AP (95% CI)	0.38 (0.04, 0.72)
		P_{AP} for interaction	0.03
		Synergy Index	2.07 (0.83, 5.02)

Multiplicative interaction:	
Caffeine (high/low) *family history (yes/no)	1.34 (0.68, 2.64); P _{multi} = 0.40
Caffeine (100mg/day) * family history (yes/no)	1.11 (0.92, 1.33); P _{multi} = 0.26

Table e-2b. Tests of interactions on the multiplicative and additive scale for the NHS

NHS			
Predictor 1	Predictor 2	HR (95% CI)	p-value
Caffeine	Smoking		
Low	Never	1.00 (reference)	
High	Never	1.05 (0.83, 1.33)	0.68
Low	Ever	0.73 (0.58, 0.91)	<0.01
High	Ever	0.57 (0.45, 0.73)	<0.0001
		Additive interaction:	
		RERI	-0.44 (-1.01, 0.12)
		AP (95% CI)	-0.25 (-0.56, -0.07)
		P _{AP} for interaction	0.12
		Synergy Index	0.64 (0.40, 1.03)
		Multiplicative interaction:	
		Caffeine (high/low) * smoking (never/ever)	0.75 (0.53, 1.07); P _{multi} = 0.11
		Caffeine (100 mg /day) * smoking categories	P _{multi} = 0.55
Caffeine	Physical Activity		
Low	Low	1.00 (reference)	
High	Low	0.85 (0.66, 1.09)	0.20
Low	High	0.80 (0.64, 1.00)	0.05
High	High	0.87 (0.68, 1.11)	0.26
		Additive interaction:	
		RERI	0.24 (-0.09, 0.57)
		AP (95% CI)	0.21 (0.03, 0.39)
		P _{AP} for interaction	0.02
		Synergy Index	No estimate
		Multiplicative interaction:	
		Caffeine(high/low) * physical activity (high/low)	1.28 (0.90, 1.81); P _{multi} = 0.17
		Caffeine (100 mg/day) * physical activity (quintiles)	P _{multi} = 0.33
Caffeine	Family History		
Low	Yes	1.00 (reference)	
High	Yes	0.80 (0.45, 1.41)	0.43

Low	No	0.43 (0.30, 0.62)	<0.0001
High	No	0.42 (0.29, 0.61)	<0.0001
Additive interaction:			
		RERI	0.55 (-0.65, 1.74)
		AP (95% CI)	0.22 (-0.17, 0.61)
		P_{AP} for interaction	0.27
		Synergy Index	1.59 (0.53, 4.77)
Multiplicative interaction:			
		Caffeine (high/low) *family history (yes/no)	1.23 (0.68, 2.22); $P_{multi} = 0.50$
		Caffeine (100mg/day) * family history (yes/no)	1.04 (0.91, 1.18); $P_{multi} = 0.62$
Smoking	PMH		
Never	Never	1.00 (reference)	
Ever	Never	0.58 (0.42, 0.79)	<0.001
Never	Ever	0.97 (0.76, 1.24)	0.80
Ever	Ever	0.63 (0.49, 0.82)	<0.001
Additive interaction:			
		RERI	-0.05 (-0.42, 0.32)
		AP (95% CI)	-0.04 (-0.32, 0.23)
		P_{AP} for interaction	0.75
		Synergy Index	No estimate
Multiplicative interaction:			
		Smoking (never/ever) * PMH use (ever/never)	1.13 (0.77, 1.64); $P_{multi} = 0.54$
		Smoking (packyears) * PMH use (ever/never)	1.00 (1.00, 1.00); $P_{multi} = 0.55$

RERI= Relative Excess Risk for Interaction

AP = attributable proportion

SI = Synergy Index

Table e-3a: Tests of interactions on the additive scale in tertiles of caffeine intake for the HPFS

Predictor 1	Predictor 2	HR (95% CI)	p-value
Caffeine	Smoking		
Tertile 1	Never	1.00 (reference)	
Tertile 2	Never	0.69 (0.53, 0.90)	<0.01
Tertile 3	Never	0.73 (0.55, 0.96)	0.02
Tertile 1	Ever	0.91 (0.70, 1.17)	0.44
Tertile 2	Ever	0.67 (0.52, 0.88)	<0.01
Tertile 3	Ever	0.46 (0.35, 0.61)	<0.0001
		Additive interaction:	
		RERI ₁	-0.55 (-1.22, 0.12)
		AP ₁ (95% CI)	-0.36 (-0.81, 0.09)
		P _{AP1} for interaction	0.11
		RERI ₂	-0.38 (-0.91, 0.15)
		AP ₂ (95% CI)	-0.17 (-0.50, 0.15)
		P _{AP2} for interaction	0.30
Caffeine	Physical activity		
Tertile 1	Low	1.00 (reference)	
Tertile 2	Low	0.90 (0.68, 1.20)	0.48
Tertile 3	Low	0.66 (0.49, 0.90)	<0.01
Tertile 1	High	1.02 (0.79, 1.31)	0.89
Tertile 2	High	0.59 (0.43, 0.79)	<0.001
Tertile 3	High	0.61 (0.45, 0.83)	<0.01
		Additive interaction:	
		RERI ₁	0.44 (-0.02, 0.90)
		AP ₁ (95% CI)	0.30 (-0.01, 0.61)
		P _{AP1} for interaction	0.06
		RERI ₂	-0.11 (-0.52, 0.31)
		AP ₂ (95% CI)	-0.07 (-0.40, 0.27)
		P _{AP2} for interaction	0.70
Caffeine	Family history		
Tertile 1	Yes	1.00 (reference)	
Tertile 2	Yes	0.57 (0.28, 1.15)	0.11
Tertile 3	Yes	0.38 (0.17, 0.85)	0.02
Tertile 1	No	0.38 (0.25, 0.59)	<0.0001
Tertile 2	No	0.28 (0.18, 0.44)	<0.0001
Tertile 3	No	0.24 (0.15, 0.38)	<0.0001
		Additive interaction:	
		RERI ₁	0.62 (-1.12, 2.36)

AP ₁ (95% CI)	0.26 (-0.37, 0.89)
<i>P</i> _{AP1} for interaction	0.42
RERI ₂	2.01 (0.19, 3.83)
AP ₂ (95% CI)	0.48 (0.14, 0.83)
<i>P</i> _{AP2} for interaction	<0.01

Table e-3b: Tests of interactions on the additive scale in tertiles of caffeine intake for the NHS

Predictor 1	Predictor 2	HR (95% CI)	p-value
Caffeine	Smoking		
Tertile 1	Never	1.00 (reference)	
Tertile 2	Never	1.08 (0.83, 1.40)	0.58
Tertile 3	Never	1.21 (0.91, 1.60)	0.19
Tertile 1	Ever	0.73 (0.54, 0.99)	<0.05
Tertile 2	Ever	0.76 (0.58, 1.01)	0.06
Tertile 3	Ever	0.58 (0.43, 0.77)	0.0001
		Additive interaction:	
		RER1	-0.51 (-1.23, 0.21)
		AP1 (95% CI)	- 0.27 (-0.67, 0.12)
		<i>P</i> _{AP1} for interaction	0.17
		RER2	-0.60 (-1.05, -0.15)
		AP2 (95% CI)	-0.35 (-0.76, 0.07)
		<i>P</i> _{AP2} for interaction	0.10
Caffeine	Physical activity		
Tertile 1	Low	1.00 (reference)	
Tertile 2	Low	1.05 (0.79, 1.39)	0.76
Tertile 3	Low	0.91 (0.67, 1.23)	0.52
Tertile 1	High	0.84 (0.63, 1.12)	0.23
Tertile 2	High	0.95 (0.71, 1.26)	0.71
Tertile 3	High	0.98 (0.72, 1.32)	0.87
		Additive interaction:	
		RER1	0.13 (-0.28, 0.54)
		AP1 (95% CI)	0.12 (-0.26, 0.50)
		<i>P</i> _{AP1} for interaction	0.53
		RER2	0.24 (-0.04, 0.52)
		AP2 (95% CI)	0.23 (-0.14, 0.60)
		<i>P</i> _{AP2} for interaction	0.22
Caffeine	Family history		
Tertile 1	Yes	1.00 (reference)	
Tertile 2	Yes	0.96 (0.50, 1.83)	0.89
Tertile 3	Yes	0.94 (0.49, 1.82)	0.86
Tertile 1	No	0.43 (0.27, 0.68)	<0.001
Tertile 2	No	0.47 (0.30, 0.75)	<0.01
Tertile 3	No	0.45 (0.28, 0.71)	<0.001
		Additive interaction:	
		RER1	-0.01 (-1.48, 1.46)
		AP1 (95% CI)	0.00 (-0.69, 0.68)
		<i>P</i> _{AP1} for interaction	0.99
		RER2	0.15 (-0.85, 1.15)
		AP2 (95% CI)	0.07 (-0.56, 0.69)

RERI= Relative Excess Risk for Interaction

AP = attributable proportion

SI = Synergy Index

Table e-4: Hazard ratios by quintiles for the HPFS using the same predictors as NHS						
	Quintiles of risk score					<i>P</i> _{trend}
	1	2	3	4	5	
HPFS						
Median risk score*	9	12	13	14	17	
Number of cases	157	146	76	125	79	
Person-years	141,009	227,704	130,443	238,171	187,723	
Hazard Ratio (95% CI)						
Risk score	1.0 (REF)	0.54 (0.43, 0.67)	0.49 (0.37, 0.65)	0.43 (0.34, 0.54)	0.33 (0.25, 0.43)	<0.0001
Linear/per point			0.87 (0.84, 0.90)			<0.0001

* In 1986 (at baseline)

^a Caffeine, smoking, physical activity, and family history of PD

Table e-5. Hazard Ratio of PD by quintiles of risk score without smoking as a risk factor for HPFS (men) and NHS (women)						
	Quintiles of risk score					<i>P</i> _{trend}
	1	2	3	4	5	
HPFS						
Median risk score*	13	16	17	18	21	
Number of cases	178	129	74	103	99	
Person-years	195,218	192,447	114,678	215,627	207,078	
Hazard Ratio (95% CI)						
Risk score ^a	1.0 (REF)	0.67 (0.53, 0.84)	0.67 (0.51, 0.88)	0.49 (0.38, 0.62)	0.50 (0.39, 0.65)	<0.0001
NHS						
Median risk score*	8	10	11	12	13	
Number of cases	107	146	102	74	105	
Person-years	239,458	467,386	345,312	283,633	391,405	
Hazard Ratio (95% CI)						
Risk score ^b	1.0 (REF)	0.68 (0.53, 0.88)	0.65 (0.49, 0.85)	0.56 (0.42, 0.75)	0.60 (0.46, 0.78)	<0.0001

* At baseline: 1986 for HPFS, 1984 for NHS

^a Caffeine, physical activity, dietary urate index, flavonoid intake, and family history of PD

^b Caffeine, physical activity, and family history of PD

Table e-6. Hazard Ratio of PD by quintiles of risk score with anthocyanin as a risk factor for HPFS (men) and NHS (women)						
	Quintiles of risk score					<i>P</i> _{trend}
	1	2	3	4	5	
HPFS						
Median risk score*	15	18	20	21	24	
Number of cases	195	97	122	95	74	
Person-years	201,958	173,341	200,617	176,187	172,947	
Hazard Ratio (95% CI)						
Risk score ^a	1.0 (REF)	0.56 (0.44, 0.72)	0.58 (0.46, 0.73)	0.51 (0.40, 0.66)	0.39 (0.30, 0.51)	<0.0001
NHS						
Median risk score*	12	15	16	17	20	
Number of cases	131	142	113	48	100	
Person-years	326,006	356,670	422,475	213,224	408,819	
Hazard Ratio (95% CI)						
Risk score ^b	1.0 (REF)	0.94 (0.74, 1.19)	0.61 (0.47, 0.78)	0.56 (0.40, 0.78)	0.55 (0.42, 0.71)	<0.0001

* At baseline: 1986 for HPFS, 1984 for NHS

^a Caffeine, physical activity, dietary urate index, anthocyanin intake, and family history of PD

^b Caffeine, physical activity, anthocyanin intake, and family history of PD