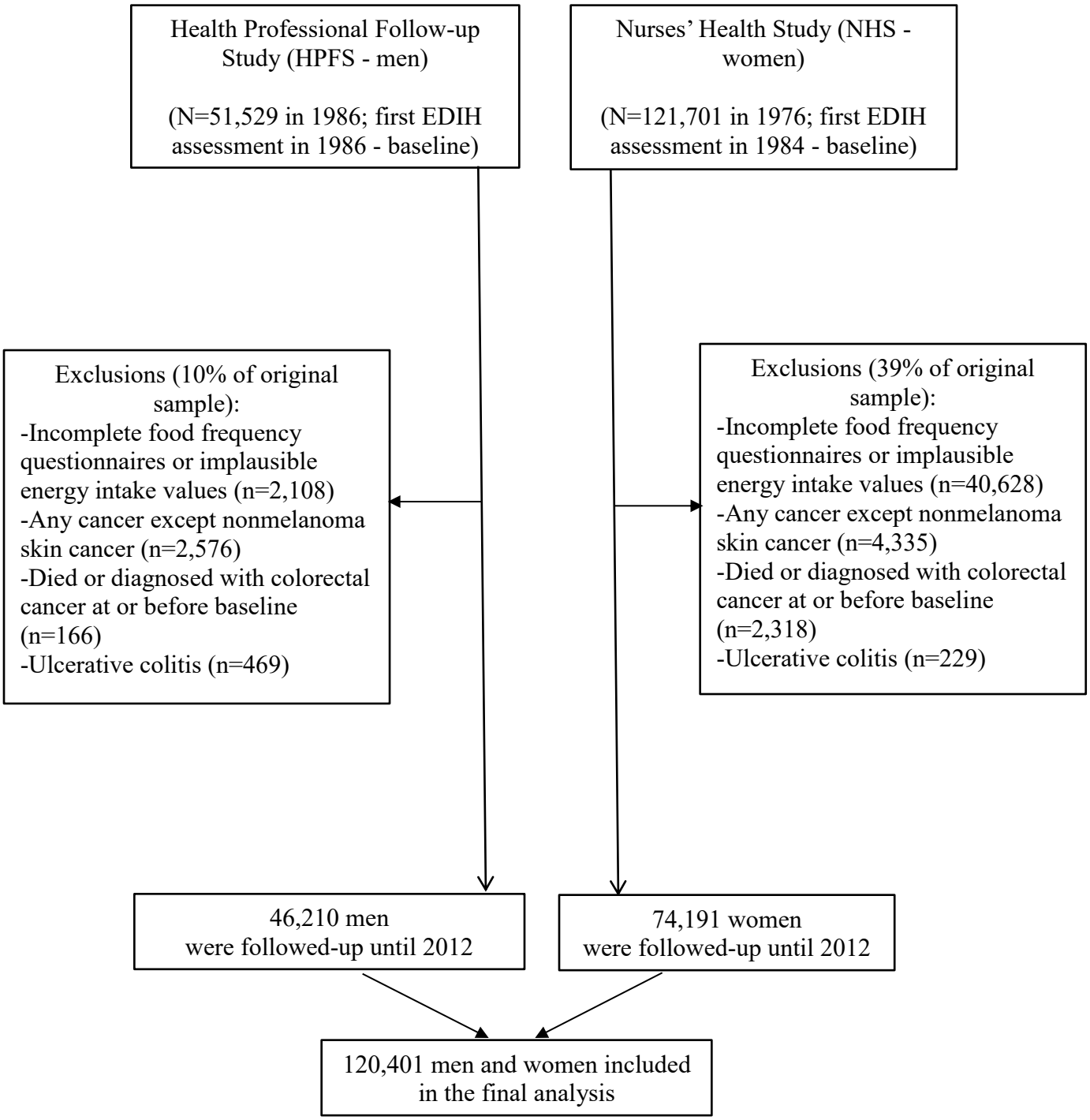
Online Supporting Material

Supplemental Figure 1. Participant flow chart



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Supplemental Table 1. Distribution of characteristics (weighted by person-years) among the **excluded participants**, in quintiles of the empirical dietary index for hyperinsulinemia (EDIH) score in the NHS (1984-2012) and the HPFS (1986-2012)[1, 2]

Characteristic	Nurses' Health Study (women) n=47,570			Health Professionals Follow-up Study (men) n=5,319		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Median EDIH score	-1.14	-0.02	1.18	-1.06	-0.03	1.04
Age, years	56.7 ± 6.2[3]	55.8 ± 6.6	54.4 ± 7.1	82.1 ± 10.0	80.9 ± 9.8	78.6 ± 10.1
Alcohol drinkers, %	75.2	63.8	53.3	68.1	61.9	48.0
Total alcohol, drinks/week, among drinkers	7.7 ± 8.1	4.9 ± 6.5	5.2 ± 6.9	10.0 ± 10.2	7.0 ± 7.1	6.5 ± 7.8
Current smoker, %	20.8	22.9	24.3	0.6	0.2	1.3
Regular aspirin use, yes, %	69.2	70.0	64.7	40.7	38.8	40.2
Family history of colorectal cancer, yes, %	20.9	17.8	18.3	3.7	6.6	4.9
History of endoscopy, yes, %	4.9	4.6	5.1	18.2	18.8	16.5
Multivitamin use, yes, %	46.7	43.3	40.7	52.9	53.9	50.8
Diabetes, yes, %	0.9	2.1	5.2	6.9	10.1	16.3
Total energy intake, Kcal/d	1846 ± 490	1651 ± 467	1827 ± 513	2221 ± 595	1842 ± 590	2118 ± 729
Dietary fiber, g/d	19.1 ± 2.0	18.1 ± 5.3	16.8 ± 5.0	28.1 ± 9.3	24.2 ± 7.4	21.1 ± 6.5
Dietary calcium, mg/d	734 ± 243	732 ± 262	687 ± 250	920 ± 342	908 ± 348	836 ± 350
Vitamin D, IU/d	205 ± 112	213 ± 117	199 ± 117	266 ± 153	267 ± 145	251 ±149
Whole grains, g/d	17.5 ± 17.0	15.5 ± 13.3	12.5 ± 12.7	37.8 ± 26.5	32.8 ± 21.4	27.0 ± 21.1
Physical activity, MET-hour/week	16.4 ± 20.1	13.5 ± 15.9	12.1 ± 15.3	38.9 ± 29.9	34.0 ± 24.4	33.9 ± 21.1
≥Median physical activity[5], %	49.5	42.8	41.8	80.1	73.2	75.8
Body mass index, kg/m^2	24.2 ± 3.6	25.2 ± 4.1	26.5 ± 5.3	24.7 ± 3.3	25.8 ± 3.7	27.5 ± 4.4
Overweight or obese, ≥25kg/m^2, %	41.6	53.3	63.3	0.6	2.2	1.3
Postmenopausal, %	76.7	74.6	67.5	NA	NA	NA
Hormone therapy use ever[4], %	49.1	48.2	48.7	NA	NA	NA

[1]Weighted by follow-up time (person-years) accrued by each participant. NA=not applicable

[2]EDIH scores were adjusted for energy intake using the residual method. Lower EDIH scores indicate insulin sensitive diets, and higher scores indicate hyperinsulinemic diets.

[3]Mean ± SD (all such values)

[4]Among postmenopausal women

[5]Median physical activity was 35.6 MET-hour/week in men and 14.1 MET-hour/week in women

Supplemental Table 2. Minimally adjusted hazard ratios and 95% confidence intervals for colorectal cancer risk in quintiles of the empirical dietary index for hyperinsulinemia (EDIH) scores among men and women[1,2,3]

	Quintile 1 (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend[4]
Colorectal cancer						
Men, cases/person-years	254/189664	234/190395	272/190593	249/190635	235/189983	
Men, HR (95%CI)	1.00	0.94 (0.79, 1.13)	1.16 (0.97, 1.38)	1.13 (0.94, 1.35)	1.29 (1.07, 1.55)	0.001
Women, cases/person-years	298/320941	291/321026	294/321112	280/321696	276/322426	
Women, HR (95%CI)	1.00	1.01 (0.85, 1.19)	1.07 (0.91, 1.26)	1.13 (0.95, 1.33)	1.30 (1.10, 1.54)	0.001
Colon cancer						
Men, cases (n=984)	207	187	213	198	179	
Men, HR (95%CI)	1.00	0.92 (0.76, 1.13)	1.11 (0.91, 1.35)	1.11 (0.91, 1.35)	1.22 (0.99, 1.50)	0.02
Women, cases (n=1129)	229	226	227	219	228	
Women, HR (95%CI)	1.00	1.00 (0.83, 1.20)	1.06 (0.88, 1.28)	1.14 (0.94, 1.37)	1.40 (1.15, 1.69)	0.0003
Proximal colon cancer						
Men, cases (n=424)	94	86	85	83	76	
Men, HR (95%CI)	1.00	0.91 (0.67, 1.22)	0.96 (0.72, 1.30)	1.02 (0.75, 1.37)	1.10 (0.81, 1.51)	0.43
Women, cases (n=714)	148	146	144	144	132	
Women, HR (95%CI)	1.00	1.01 (0.80, 1.28)	1.06 (0.84, 1.34)	1.20 (0.95, 1.52)	1.33 (1.04, 1.70)	0.009
Distal colon cancer						
Men, cases (n=354)	66	60	90	71	67	
Men, HR (95%CI)	1.00	0.99 (0.69, 1.41)	1.56 (1.13, 2.16)	1.30 (0.92, 1.83)	1.55 (1.09, 2.20)	0.004
Women, cases (n=387)	71	75	81	70	90	
Women, HR (95%CI)	1.00	1.04 (0.75, 1.44)	1.17 (0.85, 1.62)	1.10 (0.78, 1.54)	1.58 (1.14, 2.19)	0.006

Rectal cancer						
Men, cases (n=260)	47	47	59	51	56	
Men, HR (95%CI)	1.00	1.02 (0.68, 1.54)	1.36 (0.92, 2.01)	1.22 (0.82, 1.83)	1.60 (1.07, 2.38)	0.01
Women, cases (n=310)	69	65	67	61	48	
Women, HR (95%CI)	1.00	1.03 (0.73, 1.45)	1.12 (0.79, 1.58)	1.09 (0.76, 1.55)	0.96 (0.66, 1.41)	0.99

[1]EDIH scores were adjusted for total energy intake using the residual method prior to analyses. In EDIH quintiles, lower scores indicate insulin sensitive diets, and higher scores indicate hyperinsulinemic diets.
[2]Heterogeneity for risk by anatomic subsite was tested using Duplication method cause-specific Cox models (*P*-heterogeneity=0.53 among men and 0.48 among women).
[3]HR (95% CI) from Cox models were adjusted for age, alcohol intake and calendar year of the current questionnaire.
[4]The p-value for linear trend across EDIH quintiles was the p-value of the ordinal variable constructed by assigning quintile medians to all participants in the quintile. Cox models for linear trend were adjusted for all covariates listed in footnote #2

Supplemental Table 3. Multivariable-adjusted associations between the empirical dietary index for hyperinsulinemia (EDIH) score and CRC risk additionally adjusted for BMI and diabetes in men and women[1,2,3]

	Quintile 1 (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend[4]
Colorectal cancer among men						
BMI	1.00	0.94 (0.78, 1.12)	1.14 (0.96, 1.36)	1.11 (0.93, 1.33)	1.31 (1.09, 1.58)	0.001
Diabetes	1.00	0.94 (0.78, 1.12)	1.14 (0.95, 1.36)	1.10 (0.92, 1.32)	1.29 (1.07, 1.56)	0.002
Colorectal cancer among women						
BMI	1.00	0.99 (0.84, 1.16)	1.04 (0.88, 1.23)	1.07 (0.90, 1.26)	1.19 (1.00, 1.42)	0.04
Diabetes	1.00	0.99 (0.84, 1.17)	1.05 (0.89, 1.24)	1.08 (0.91, 1.28)	1.21 (1.02, 1.44)	0.02
Colon cancer among men						
BMI	1.00	0.92 (0.75, 1.13)	1.10 (0.90, 1.33)	1.10 (0.90, 1.34)	1.24 (1.01, 1.53)	0.01
Diabetes	1.00	0.92 (0.75, 1.13)	1.09 (0.90, 1.33)	1.09 (0.89, 1.33)	1.22 (0.99, 1.51)	0.02
Colon cancer among women						
BMI	1.00	0.98 (0.82, 1.19)	1.03 (0.85, 1.24)	1.08 (0.89, 1.31)	1.30 (1.07, 1.58)	0.006
Diabetes	1.00	0.99 (0.82, 1.19)	1.03 (0.86, 1.25)	1.09 (0.90, 1.32)	1.31 (1.08, 1.59)	0.004
Proximal colon cancer among men						
BMI	1.00	0.90 (0.67, 1.22)	0.95 (0.70, 1.28)	1.00 (0.74, 1.36)	1.15 (0.84, 1.57)	0.34
Diabetes	1.00	0.90 (0.67, 1.22)	0.94 (0.70, 1.27)	1.00 (0.74, 1.35)	1.13 (0.82, 1.54)	0.39
Proximal colon cancer among women						
BMI	1.00	1.00 (0.79, 1.26)	1.04 (0.82, 1.32)	1.16 (0.91, 1.47)	1.26 (0.98, 1.62)	0.04
Diabetes	1.00	1.00 (0.79, 1.26)	1.04 (0.82, 1.32)	1.16 (0.91, 1.47)	1.26 (0.98, 1.62)	0.04
Distal colon cancer among men						
BMI	1.00	0.97 (0.68, 1.39)	1.54 (1.11, 2.14)	1.26 (0.89, 1.78)	1.57 (1.10, 2.24)	0.005

Diabetes	1.00	0.97 (0.68, 1.39)	1.56 (1.12, 2.16)	1.27 (0.90, 1.80)	1.61 (1.13, 2.30)	0.003
Distal colon cancer among women						
BMI	1.00	1.02 (0.73, 1.42)	1.12 (0.81, 1.55)	1.01 (0.72, 1.43)	1.41 (1.01, 1.97)	0.05
Diabetes	1.00	1.03 (0.74, 1.43)	1.14 (0.82, 1.58)	1.04 (0.74, 1.46)	1.46 (1.05, 2.03)	0.03
Rectal cancer among men						
BMI	1.00	1.00 (0.66, 1.51)	1.34 (0.91, 1.99)	1.17 (0.78, 1.76)	1.61 (1.07, 2.41)	0.02
Diabetes	1.00	1.00 (0.66, 1.50)	1.33 (0.90, 1.98)	1.16 (0.77, 1.74)	1.58 (1.05, 2.36)	0.02
Rectal cancer among women						
BMI	1.00	0.99 (0.70, 1.40)	1.07 (0.76, 1.51)	1.00 (0.70, 1.43)	0.83 (0.56, 1.23)	0.42
Diabetes	1.00	1.00 (0.71, 1.42)	1.10 (0.78, 1.55)	1.04 (0.73, 1.48)	0.88 (0.60, 1.30)	0.65

[1]NSAIDs=non-steroidal anti-inflammatory drugs. Values are hazards ratios (95% confidence intervals)

[2]EDIH scores were adjusted for total energy intake using the residual method. In EDIH quintiles, lower scores indicate insulin sensitive diets, and higher scores indicate hyperinsulinemic diets.

[3]Cox models were adjusted for race, family history of cancer, history of endoscopy, multivitamin use, total alcohol intake, physical activity, pack-years of smoking, regular aspirin use, regular NSAIDs use, and additionally for menopausal status, and postmenopausal hormone use in women.

[4]The p-value for linear trend across EDIH quintiles was the p-value of the ordinal variable constructed by assigning quintile medians to all participants in the quintile. Cox models for linear trend were adjusted for all covariates listed in footnote #3.

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Supplemental Table 4. Hazard ratios of the association between the empirical dietary pattern for hyperinsulinemia score and colorectal cancer risk in combined categories of physical activity and body weight[1,2]

	Quintiles of the empirical dietary pattern for hyperinsulinemia (EDIH) score					
Subgroups	Quintile 1 (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-trend[3]
Men						
High activity and lean, n cases=296	1.00	0.60 (0.42, 0.87)	0.79 (0.56, 1.12)	0.92 (0.64, 1.32)	0.99 (0.67, 1.45)	0.84
High activity and overweight/obese, n cases=308	1.00	1.12 (0.77, 1.63)	1.19 (0.82, 1.74)	1.09 (0.74, 1.61)	1.16 (0.79, 1.71)	0.53
Low activity and lean, n cases=308	1.00	1.21 (0.84, 1.74)	1.10 (0.75, 1.60)	1.24 (0.84, 1.82)	1.89 (1.30, 2.76)	0.002
Low activity and overweight/obese, n cases=330	1.00	0.98 (0.65, 1.48)	1.49 (1.03, 2.17)	1.27 (0.87, 1.86)	1.45 (0.98, 2.15)	0.03
Women						
High activity and lean, n cases=265	1.00	0.98 (0.70, 1.37)	0.89 (0.62, 1.29)	1.29 (0.89, 1.87)	0.80 (0.49, 1.30)	0.88
High activity and overweight/obese, n cases=354	1.00	0.85 (0.61, 1.20)	1.06 (0.76, 1.47)	0.68 (0.47, 0.99)	1.09 (0.78, 1.54)	0.88
Low activity and lean, n cases=315	1.00	0.96 (0.67, 1.36)	1.19 (0.84, 1.67)	1.10 (0.76, 1.59)	1.22 (0.83, 1.80)	0.23
Low activity and overweight/obese, n cases=505	1.00	1.09 (0.79, 1.51)	0.95 (0.69, 1.32)	1.26 (0.93, 1.72)	1.41 (1.03, 1.92)	0.009

[1]Activity was classified based on the sex-specific physical activity median: at or above the median as active and below the median as sedentary (median physical activity was 24.8 MET-hours/week in men and 13.4 MET-hours/week in women). Body weight was classified based on BMI categories as follows: normal weight, <25 kg/m^2 and overweight/obese as ≥25 kg/m^2. P-values for the 3-way interaction between the EDIH score, physical activity and BMI were 0.20 in men and 0.09 in women.

[2]All analyses were conducted using Cox models Cox models for linear trend were adjusted for all covariates listed in footnote #2.