Online-Only Supplementary Material.

Prevalent diabetes and risk of total, colorectal, prostate, and breast cancers in an ageing population: meta-analysis of individual participant data from cohorts of the CHANCES consortium

Amina Amadou, Heinz Freisling[#], et al.

Correspondence:

Heinz Freisling, PhD

International Agency for Research on Cancer (IARC/WHO),

Nutrition and Metabolism Branch

150 cours Albert Thomas

69372 Lyon CEDEX 08, France

Off. +33 472 738 664

Fax +33(0)472 738 361

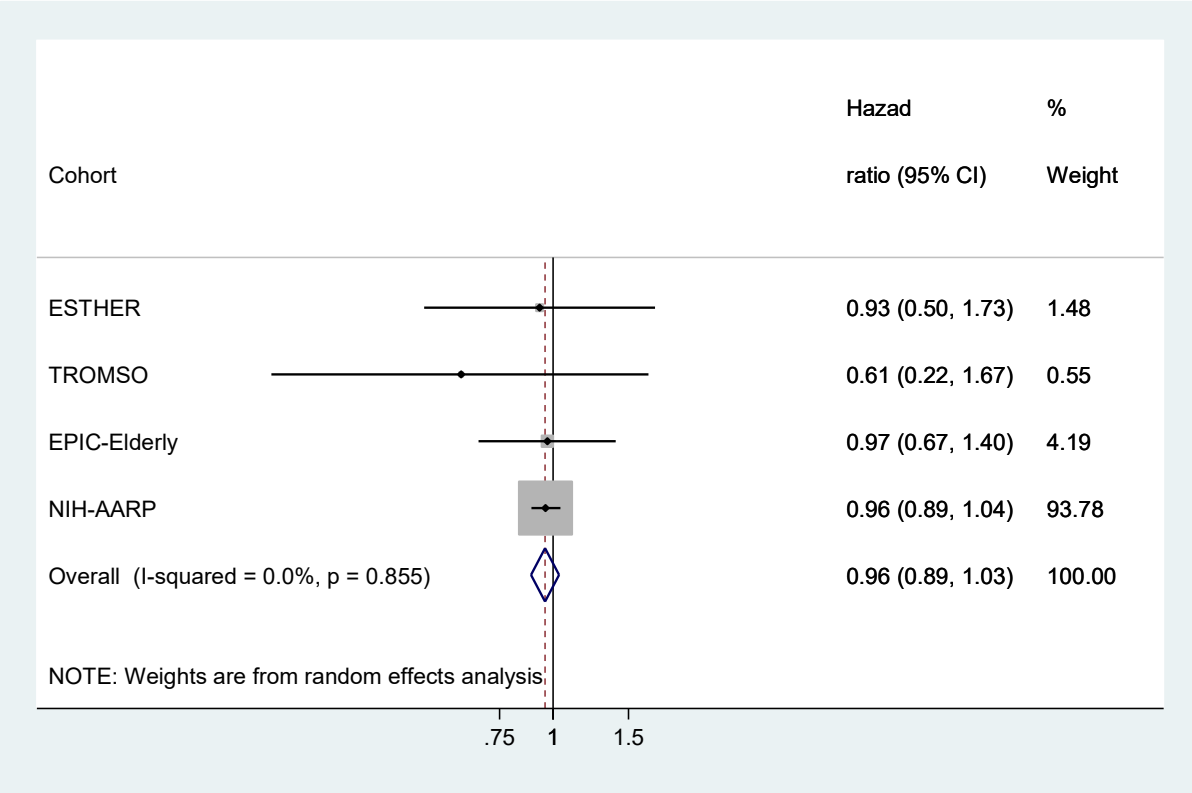
E-mail: freislingh@iarc.fr

https://orcid.org/0000-0001-8648-4998

Supplementary Text 1:

Power calculation for observed associations using the R package 'powerSurvEpi' available at **https://cran.r-project.org/web/packages/powerSurvEpi/powerSurvEpi.pdf**

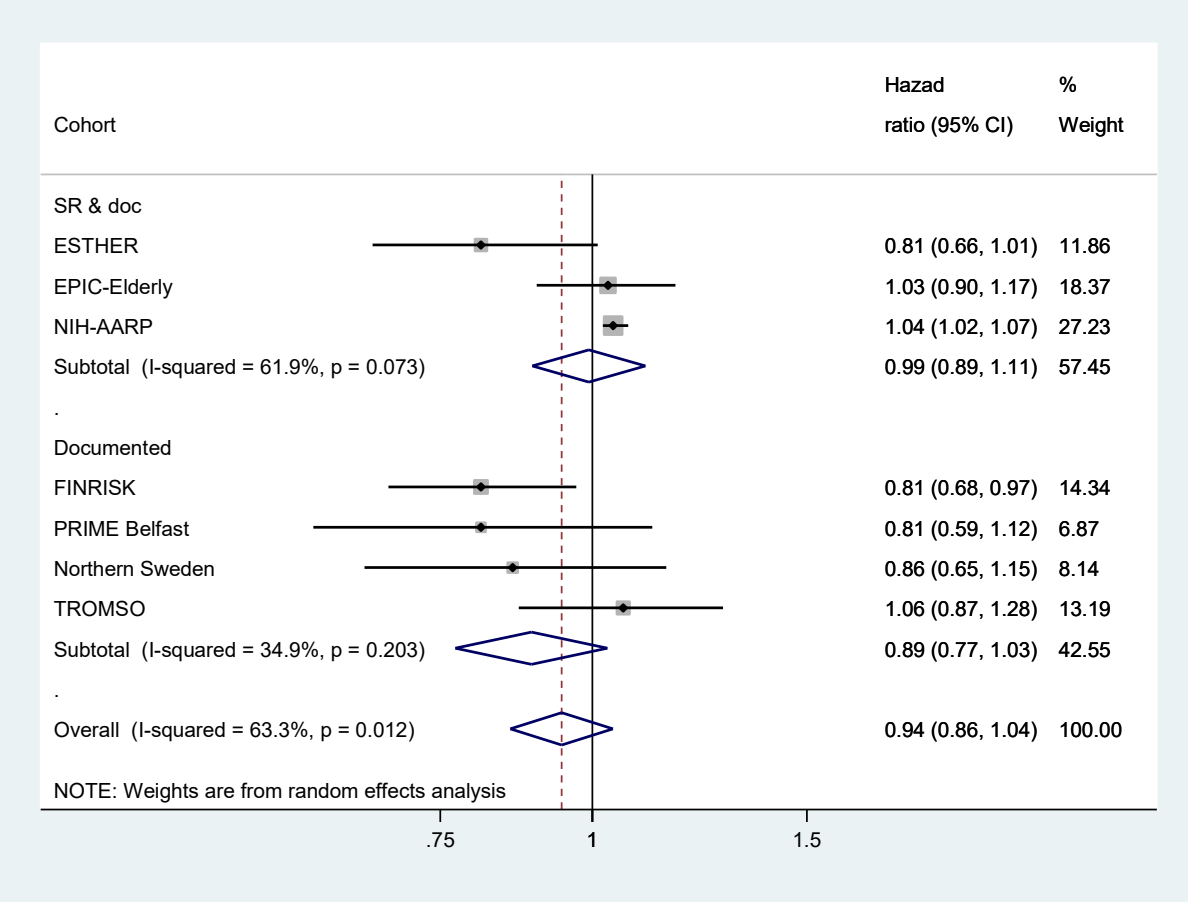
A posteriori power calculations for observed hazard ratios indicated that our study was sufficiently powered (≥80%) for total cancer (men and women combined), colorectal cancer in men, and prostate cancer, but under-powered to detect the observed hazard ratios (or less extreme) for total cancer in men (77%), total cancer women (66%), colorectal cancer in women (69%), and breast cancer in women (25%). As for interaction analysis, shown in Supplementary Tables 2-5, only prostate cancer across categories of BMI was sufficiently powered (81%). All other interaction analyses had a power of 36% or less.



Supplementary Figure 1: Random effects meta-analysis of the association between diabetes and postmenopausal breast cancer risk.

Models were adjusted for country (EPIC-Elderly only), age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), vigorous physical activity (yes/no), and menopausal hormone therapy.

The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CI). Diamonds represent the combined HRs and 95% CI.



Supplementary Figure 2: Random effects meta-analysis of the association between diabetes and total cancer risk by diabetes ascertainment (self-reported/mixed vs. documented).

Models were adjusted for country (EPIC-Elderly only), age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), and vigorous physical activity (yes/no).

The size of each box indicates the relative weight of each study in the meta-analysis; the horizontal bars show the 95% confidence intervals (CI). Diamonds represent the combined HRs and 95% CI.

Supplementary Table 1: Selected characteristics at recruitment by history of diabetes in all cohorts combined

Characteristic	History of diabetes	
	No (n=600,754 [90.7%])	Yes (n=61,587 ([9.3%])
Age (years), P50 (P25-P75)	62.1 (56.9-66.4)	63.4 (58.5-67.1)
BMI* (kg/m²)	26.9 ± 4.9	29.7 ± 5.9
Missing n, (%)	62,612 (10.4)	6,353 (10.2)
Alcohol intake* (g per day)	12.8 ± 36.3	8.2 ± 32.0
Missing n, (%)	4,376 (0.7)	481 (0.8)
Smoking status		
Never	223,254 (37.1)	20,292 (32.9)
Ever	356,649 (59.4)	39,084 (63.5)
Missing, n (%)	20,851 (3.5)	2,211 (3.6)
Vigorous physical activity		
No	296,553 (49.4)	34,900 (56.7)
Yes	250,046 (41.6)	21,298 (34.6)
Missing, n (%)	54,155 (9.0)	5,389 (8.7)
School level		
Primary or less	48,369 (8.1)	6,803 (11.1)
> Primary - < college or university	159,227 (26.5)	18,358 (29.8)
College or university	377,286 (62.8)	34,397 (55.8)
Missing	15,872 (2.6)	2,029 (3.3)
Total cancer		
No	497,464 (82.8)	50,473 (82.0)
Yes	103,290 (17.2)	11,114 (18.0)
Colorectal cancer		
No	544,899 (98.4)	55,739 (98.0)
Yes	8,664 (1.6)	1,122 (2.0)
Prostate cancer		
No	519,428 (95.5)	54,209 (96.6)
Yes	24,430 (4.5)	1,894 (3.4)
Breast cancer		
No	542,703 (98.0)	56,046 (98.6)
Yes	10,860 (2.0)	815 (1.4)

Values are arithmetic means, SD (standard deviation), unless other specified.

* Mean without imputation.

Supplementary Table 2: Sensitivity analyses using fixed effect meta-analysis and pooled analysis

	Fixed effect meta-analysis			**Pooled analysis**	**Pooled analysis ****
	HR (95% CI)	I^2	*P*-het.	HR (95% CI)	HR (95% CI)
Total cancer					
Overall	1.03 (1.01-1.05)	63.3%	0.012	1.04 (1.02-1.06)	1.04 (1.02-1.07)
Men	1.01 (0.98-1.03)	39.5%	0.128	1.01 (0.99-1.04)	1.02 (0.99-1.04)
Women	1.11 (1.07-1.15)	59.3%	0.031	1.11 (1.07-1.16)	1.13 (1.09-1.18)
Colorectal cancer					
Overall	1.22 (1.14-1.30)	51.8%	0.101	1.22 (1.15-1.30)	1.22 (1.14-1.30)
Men	1.17 (1.08-1.26)	0.0%	0.395	1.18 (1.09-1.27)	1.18 (1.09-1.27)
Women	1.33 (1.19-1.49)	46.0%	0.135	1.34 (1.19-1.51)	1.32 (1.17-1.48)
Prostate cancer	0.81 (0.77-0.85)	0.0%	0.961	0.81 (0.77-0.85)	0.81 (0.77-0.85)
*Breast cancer	0.96 (0.89-1.03)	0.0%	0.855	0.96 (0.89-1.02)	0.96 (0.89-1.03)

P-het, heterogeneity associated with *I*-squared (I^2).

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), and vigorous physical activity (yes/no).

*Further adjusted for hormone replacement therapy.

** Multivariable adjusted models excluding participants with missing values; without any imputation of continuous data: percentage of missing data of alcohol and BMI equal to 0.7% and 10% of the total data, respectively.

Supplementary Table 3: Association between diabetes status and cancer risk by age groups

	Age (years)				
	< 60 HR (98% CI)	**60-65** HR (98% CI)	**65-70** HR (98% CI)	**≥ 70** HR (98% CI)	*P* interaction
Total cancer					
Overall	1.06 (1.00-1.12)	1.01 (0.97-1.06)	1.05 (1.01-1.09)	1.02 (0.92-1.13)	0.261
Men	1.04 (0.97-1.11)	1.00 (0.95-1.06)	1.02 (0.97-1.06)	1.00 (0.89-1.12)	0.879
Women	1.10 (1.01-1.21)	1.05 (0.97-1.14)	1.17 (1.09-1.26)	1.08 (0.91-1.30)	0.085
Colorectal cancer					
Overall	1.26 (1.06-1.05)	1.13 (0.98-1.30)	1.28(1.14-1.43)	1.12 (0.83-1.51)	0.279
Men	1.26 (1.03-1.55)	1.16 (0.98-1.37)	1.16 (1.01-1.33)	1.13 (0.79-1.62)	0.797
Women	1.25 (0.89-1.75)	1.06 (0.81-1.39)	1.58(1.30-1.91)	1.08 (0.64-1.83)	0.045
Prostate cancer	0.87 (0.76-0.98)	0.76 (0.69-0.85)	0.83 (0.76-0.90)	0.81 (0.63-1.02)	0.241
*Breast cancer	0.95 (0.80-1.14)	0.95 (0.82-1.12)	0.99 (0.86-1.14)	0.93 (0.63-1.38)	0.827

HR, hazard ratios and 98% confidence intervals (CI) accounting for multiple testing using Bonferroni correction (100 – 5 /k %); k=24); $P < 0.002$.

Models were adjusted for country (EPIC-elderly only), age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), and vigorous physical activity (yes/no).

*Further adjusted for hormone replacement therapy.

Supplementary Table 4: Association between diabetes status and cancer risk by World Health Organization (WHO) body mass index (BMI) categories.

	BMI < 25 kg/m^2 HR (98% CI)	**BMI 25-<30 kg/m^2** HR (98% CI)	**BMI ≥ 30 kg/m^2** HR (98% CI)	*P* interaction
Total cancer				
Overall	1.01 (0.95-1.07)	1.04 (1.00-1.07)	1.06 (1.01-1.10)	0.044
Men	0.97 (0.91-1.04)	1.02 (0.98-1.06)	1.02 (0.97-1.07)	0.421
Women	1.12 (1.00-1.24)	1.10 (1.02-1.18)	1.11 (1.04-1.19)	0.176
Colorectal cancer				
Overall	1.34 (1.12-1.59)	1.19 (1.06-1.33)	1.20 (1.06-1.36)	0.847
Men	1.33 (1.08-1.63)	1.15 (1.01-1.31)	1.16 (1.00-1.35)	0.225
Women	1.37 (1.00-1.89)	1.32 (1.05-1.66)	1.28 (1.05-1.57)	0.650
Prostate cancer	**0.94 (0.83-1.07)**	**0.77 (0.71-0.83)**	**0.81 (0.73-0.89)**	**< 0.001**
*Breast cancer	1.01 (0.81-1.25)	0.90 (0.77-1.05)	0.97 (0.86-1.10)	0.833

HR, hazard ratios and 98% confidence intervals (CI) accounting for multiple testing using Bonferroni correction (100 – 5 /k %); k=24); $P < 0.002$.

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), and vigorous physical activity (yes/no).

*Further adjusted for hormone replacement therapy.

Supplementary Table 5: Association between diabetes status and cancer risk by vigorous physical activity

	Vigorous physical activity = no HR (98% CI)	**Vigorous physical activity = yes** HR (98% CI)	*P* interaction
Total cancer			
Overall	1.06 (1.02-1.09)	1.02 (0.98-1.06)	0.019
Men	1.02 (0.98-1.06)	1.00 (0.96-1.05)	0.253
Women	1.14 (1.08-1.21)	1.08 (0.99-1.17)	0.032
Colorectal cancer			
Overall	1.23 (1.12-1.35)	1.21 (1.07-1.37)	0.448
Men	1.15 (1.02-1.30)	1.21 (1.05-1.39)	0.739
Women	1.40 (1.19-1.65)	1.21 (0.94-1.57)	0.284
Prostate cancer	0.82 (0.76-0.88)	0.80 (0.74-0.87)	0.780
Breast cancer*	0.98 (0.88-1.09)	1.05 (0.90-1.22)	0.738

HR, hazard ratios and 98% confidence intervals (CI) accounting for multiple testing using Bonferroni correction (100 – 5 /k %); k=24); $P < 0.002$.

Models were adjusted for country, age (years), smoking status (never/ever), educational level (primary or less/primary or less than college or university/college or university), alcohol consumption (g/day), BMI, (kg/m^2), and vigorous physical activity (yes/no).

*Further adjusted for hormone replacement therapy.