**Type 2 diabetes prevention diet and hepatocellular carcinoma risk in U.S. men and women**

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**Supplementary Table 1. Characteristics of participants according to dietary diabetes risk reduction score in the Nurses’ Health Study and the Health Professionals Follow-up Study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dietary diabetes risk reduction score** | | | |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Women (NHS)** |  |  |  |  |
| Age (year)\* | 54.9(10.6) | 58.9(10.8) | 62.4(10.7) | 66.3(10.1) |
| White, % | 96.8 | 97.4 | 97.7 | 97.9 |
| Body mass index, kg/m2 | 25.6(5.1) | 25.2(4.6) | 24.9(4.2) | 24.3(3.9) |
| Physical activity, METS-hours/week | 12.1(15.9) | 13.9(15.5) | 16.6(16.7) | 21.5(19.8) |
| Type 2 diabetes, % | 6.8 | 6.4 | 5.5 | 4.3 |
| Regular aspirin use, % | 40.4 | 40.6 | 40.7 | 39.1 |
| Smoking status |  |  |  |  |
| Past smoking, % | 30.3 | 36.1 | 42.1 | 49.8 |
| Current smoking, % | 17.0 | 16.9 | 14.4 | 11.0 |
| Food and nutrient intakes |  |  |  |  |
| Alcohol, g/day | 4.5(8.4) | 5.7(9.4) | 6.6(9.8) | 7.2(9.4) |
| Glycemic index, GI | 54.4(2.8) | 52.8(3.2) | 51.6(3.2) | 50.1(2.9) |
| Cereal fiber (g/day) | 2.9(1.3) | 3.6(1.6) | 4.2(1.9) | 5.0(2.2) |
| Ratio of polyunsaturated to saturated fats, P:S | 0.40(0.11) | 0.45(0.12) | 0.50(0.13) | 0.59(0.16) |
| Trans fat (% energy) | 2.2(0.5) | 2.0(0.5) | 1.8(0.5) | 1.5(0.4) |
| Sugar-sweetened beverage intake (servings/week) | 4.7(5.5) | 2.5(3.4) | 1.3(2.1) | 0.5(1.0) |
| Nut intake (servings/week) | 0.4(0.6) | 0.6(1.0) | 0.9(1.4) | 1.6(2.1) |
| Coffee intake (cups/day) | 1.6(1.5) | 2.2(1.6) | 2.5(1.6) | 2.7(1.6) |
| Red and processed meat intake (servings/day) | 1.7(0.8) | 1.4(0.6) | 1.1(0.5) | 0.7(0.4) |
| AHEI-2010 | 42.3(7.8) | 47.2(7.6) | 52.5(7.7) | 60.3(8.2) |
| **Men (HPFS)** |  |  |  |  |
| Age (year)\* | 63.8(12.5) | 66.0(12.4) | 67.3(12.1) | 68.2(11.7) |
| White, % | 95.2 | 95.8 | 95.9 | 96.5 |
| Body mass index, kg/m2 | 26.1(3.8) | 26.0(3.5) | 25.7(3.4) | 25.3(3.3) |
| Physical activity, METS-hours/week | 23.6(25.6) | 26.4(26.7) | 29.3(27.8) | 34.7(31.2) |
| Type 2 diabetes, % | 4.3 | 4.0 | 3.8 | 3.3 |
| Regular aspirin use, % | 26.3 | 29.9 | 32.2 | 35.2 |
| Smoking status |  |  |  |  |
| Past smoking, % | 27.5 | 33.2 | 36.3 | 39.9 |
| Current smoking, % | 6.2 | 5.5 | 4.3 | 3.0 |
| Food and nutrient intakes |  |  |  |  |
| Alcohol, g/day | 9.0(12.9) | 11.2(14.6) | 11.8(14.5) | 12.1(14.1) |
| Glycemic index, GI | 54.8(2.4) | 53.4(2.8) | 52.6(2.9) | 51.5(2.9) |
| Cereal fiber (g/day) | 4.9(2.0) | 5.8(2.6) | 6.9(3.4) | 8.4(4.2) |
| Ratio of polyunsaturated to saturated fats, P:S | 0.47(0.11) | 0.54(0.13) | 0.63(0.16) | 0.79(0.22) |
| Trans fat (% energy) | 1.7(0.5) | 1.5(0.5) | 1.3(0.4) | 1.0 (0.4) |
| Sugar-sweetened beverage intake (servings/week) | 4.7(5.0) | 2.5(3.3) | 1.5(2.3) | 0.6(1.2) |
| Nut intake (servings/week) | 0.9(1.3) | 1.4(1.8) | 1.8(2.4) | 2.7(3.2) |
| Coffee intake (cups/day) | 1.4(1.4) | 1.9(1.6) | 2.0(1.6) | 2.2(1.6) |
| Red and processed meat intake (servings/day) | 1.6(0.8) | 1.3(0.7) | 0.9(0.6) | 0.5(0.4) |
| AHEI-2010 | 43.6(7.3) | 50.1(7.2) | 56.5(7.6) | 64.8(8.1) |

Values were means (SD) or percentages and were standardized to the age distribution of the study population.

METS, Metabolic equivalent tasks. AHEI-2010, Alternate Healthy Eating Index-2010,

\* Value was not age adjusted.

**Supplementary Table 2. Associations between components in dietary diabetes risk reduction score and risk of hepatocellular carcinoma in the Nurses’ Health Study**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Components in dietary diabetes risk reduction score, HR (95% CI)** | | | | ***P*trend** |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Glycemic index (GI)** |  |  |  |  |  |
| Number of cases | 14 | 25 | 22 | 24 |  |
| Age-adjusted\* | 1 (Ref) | 1.54 (0.80 to 2.98) | 1.40 (0.71 to 2.75) | 1.81 (0.93 to 3.52) | 0.11 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.60 (0.82 to 3.10) | 1.45 (0.73 to 2.88) | 1.80 (0.91 to 3.54) | 0.13 |
| **Cereal ﬁber** |  |  |  |  |  |
| Number of cases | 13 | 18 | 23 | 31 |  |
| Age-adjusted\* | 1 (Ref) | 0.86 (0.41 to 1.80) | 0.79 (0.38 to 1.62) | 0.83 (0.41 to 1.68) | 0.69 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.97 (0.46 to 2.07) | 0.91 (0.43 to 1.94) | 1.03 (0.49 to 2.19) | 0.86 |
| **P:S** |  |  |  |  |  |
| Number of cases | 11 | 31 | 16 | 27 |  |
| Age-adjusted\* | 1 (Ref) | 1.68 (0.82 to 3.44) | 0.70 (0.31 to 1.56) | 0.98 (0.46 to 2.09) | 0.30 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.77 (0.86 to 3.67) | 0.76 (0.34 to 1.73) | 1.13 (0.52 to 2.47) | 0.54 |
| **Trans fat** |  |  |  |  |  |
| Number of cases | 26 | 29 | 19 | 11 |  |
| Age-adjusted\* | 1 (Ref) | 1.27 (0.75 to 2.17) | 0.98 (0.54 to 1.77) | 0.81 (0.39 to 1.68) | 0.52 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.21 (0.71 to 2.08) | 0.93 (0.50 to 1.71) | 0.75 (0.35 to 1.57) | 0.39 |
| **SSBs** |  |  |  |  |  |
| Number of cases | 21 | 23 | 19 | 22 |  |
| Age-adjusted\* | 1 (Ref) | 0.88 (0.48 to 1.60) | 0.80 (0.43 to 1.50) | 1.21 (0.66 to 2.22) | 0.32 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.93 (0.51 to 1.69) | 0.85 (0.45 to 1.60) | 1.22 (0.65 to 2.28) | 0.37 |
| **Nut intake** |  |  |  |  |  |
| Number of cases | 21 | 18 | 18 | 28 |  |
| Age-adjusted\* | 1 (Ref) | 0.75 (0.40 to 1.42) | 0.80 (0.42 to 1.51) | 1.02 (0.58 to 1.81) | 0.54 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.80 (0.42 to 1.53) | 0.91 (0.47 to 1.74) | 1.24 (0.67 to 2.28) | 0.23 |
| **Coffee intake** |  |  |  |  |  |
| Number of cases | 24 | 24 | 23 | 14 |  |
| Age-adjusted\* | 1 (Ref) | 0.77 (0.44 to 1.36) | 0.90 (0.51 to 1.60) | 0.63 (0.32 to 1.22) | 0.22 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.75 (0.42 to 1.34) | 0.87 (0.48 to 1.57) | 0.57 (0.29 to 1.13) | 0.14 |
| **Red and processed meat** |  |  |  |  |  |
| Number of cases | 26 | 23 | 22 | 14 |  |
| Age-adjusted\* | 1 (Ref) | 1.06 (0.60 to 1.86) | 1.14 (0.64 to 2.03) | 1.08 (0.55 to 2.12) | 0.76 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.02 (0.58 to 1.81) | 1.09 (0.60 to 1.97) | 0.99 (0.49 to 2.00) | 0.97 |

HR, Hazard Ratio; CI, Confidence Interval; Ref, reference group; P:S, ratio of polyunsaturated to saturated fats; SSBs, sugar-sweetened beverages.

**\***Adjusted for age (in months) and study period (two-year interval).

**\*\***Adjusted for age (in months), study period (two-year interval), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current smoking), body mass index (kg/m2, continuous), aspirin use (no, yes), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).

**Supplementary Table 3. Associations between components in dietary diabetes risk reduction score and risk of hepatocellular carcinoma in the Health Professionals Follow-up Study**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Components in dietary diabetes risk reduction score, HR (95% CI)** | | | | ***P*trend** |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Glycemic index (GI)** |  |  |  |  |  |
| Number of cases | 18 | 23 | 17 | 17 |  |
| Age-adjusted\* | 1 (Ref) | 1.32 (0.71 to 2.46) | 1.04 (0.53 to 2.04) | 1.18 (0.60 to 2.30) | 0.77 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.39 (0.74 to 2.61) | 1.13 (0.58 to 2.23) | 1.30 (0.65 to 2.59) | 0.55 |
| **Cereal ﬁber** |  |  |  |  |  |
| Number of cases | 20 | 21 | 23 | 11 |  |
| Age-adjusted\* | 1 (Ref) | 0.90 (0.48 to 1.67) | 0.91 (0.50 to 1.67) | 0.44 (0.21 to 0.93) | 0.03 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.93 (0.49 to 1.75) | 1.00 (0.53 to 1.87) | 0.55 (0.25 to 1.18) | 0.15 |
| **P:S** |  |  |  |  |  |
| Number of cases | 20 | 18 | 22 | 15 |  |
| Age-adjusted\* | 1 (Ref) | 0.79 (0.42 to 1.50) | 0.94 (0.51 to 1.74) | 0.59 (0.30 to 1.16) | 0.17 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.83 (0.43 to 1.59) | 1.01 (0.54 to 1.89) | 0.66 (0.33 to 1.32) | 0.31 |
| **Trans fat** |  |  |  |  |  |
| Number of cases | 18 | 24 | 9 | 24 |  |
| Age-adjusted\* | 1 (Ref) | 1.46 (0.79 to 2.71) | 0.52 (0.23 to 1.16) | 1.33 (0.71 to 2.47) | 0.78 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.42 (0.76 to 2.65) | 0.47 (0.21 to 1.07) | 1.27 (0.67 to 2.42) | 0.89 |
| **SSBs** |  |  |  |  |  |
| Number of cases | 17 | 18 | 24 | 16 |  |
| Age-adjusted\* | 1 (Ref) | 1.09 (0.55 to 2.13) | 1.44 (0.77 to 2.71) | 1.28 (0.64 to 2.56) | 0.53 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.13 (0.57 to 2.25) | 1.50 (0.79 to 2.86) | 1.27 (0.62 to 2.60) | 0.61 |
| **Nut intake** |  |  |  |  |  |
| Number of cases | 22 | 19 | 17 | 17 |  |
| Age-adjusted\* | 1 (Ref) | 0.89 (0.48 to 1.65) | 0.70 (0.37 to 1.33) | 0.65 (0.34 to 1.22) | 0.19 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.85 (0.45 to 1.59) | 0.64 (0.33 to 1.23) | 0.56 (0.29 to 1.09) | 0.09 |
| **Coffee intake** |  |  |  |  |  |
| Number of cases | 14 | 25 | 21 | 15 |  |
| Age-adjusted\* | 1 (Ref) | 1.36 (0.70 to 2.62) | 1.18 (0.59 to 2.33) | 0.98 (0.47 to 2.03) | 0.73 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.26 (0.64 to 2.45) | 0.98 (0.48 to 1.99) | 0.82 (0.39 to 1.75) | 0.38 |
| **Red and processed meat** |  |  |  |  |  |
| Number of cases | 9 | 17 | 31 | 18 |  |
| Age-adjusted\* | 1 (Ref) | 1.91 (0.85 to 4.29) | 3.71 (1.76 to 7.83) | 2.17 (0.97 to 4.84) | 0.05 |
| Multivariable-adjusted\*\* | 1 (Ref) | 1.67 (0.74 to 3.80) | 3.23 (1.51 to 6.89) | 1.69 (0.74 to 3.88) | 0.24 |

HR, Hazard Ratio; CI, Confidence Interval; Ref, reference group; P:S, ratio of polyunsaturated to saturated fats; SSBs, sugar-sweetened beverages.

**\***Adjusted for age (in months) and study period (two-year interval).

**\*\***Adjusted for age (in months), study period (two-year interval), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current smoking), body mass index (kg/m2, continuous), aspirin use (yes, no), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).

**Supplementary Table 4.** **Dietary diabetes risk reduction score and risk of cirrhosis in Nurses’ Health Study and Health Professionals Follow-up Study**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Dietary diabetes risk reduction score, HR (95% CI)** | | | | ***P*trend** |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |  |
| **Women (NHS)** |  |  |  |  |  |
| Number of cases (N=139) | 33 | 36 | 46 | 24 |  |
| Age-adjusted\* | 1 (Ref) | 0.82 (0.51 to 1.33) | 0.71 (0.45 to 1.12) | 0.48 (0.28 to 0.83) | 0.007 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.81 (0.50 to 1.31) | 0.69 (0.43 to 1.10) | 0.48 (0.27 to 0.84) | 0.008 |
| Multivariable-adjusted¶ | 1 (Ref) | 0.81 (0.50 to 1.31) | 0.70 (0.44 to 1.12) | 0.49 (0.28 to 0.86) | 0.01 |
| **Men (HPFS)** |  |  |  |  |  |
| Number of cases (N=40) | 13 | 13 | 8 | 6 |  |
| Age-adjusted\* | 1 (Ref) | 0.97 (0.45 to 2.10) | 0.44 (0.18 to 1.07) | 0.49 (0.18 to 1.30) | 0.05 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.91 (0.41 to 1.99) | 0.50 (0.20 to 1.23) | 0.60 (0.22 to 1.63) | 0.16 |
| Multivariable-adjusted¶ | 1 (Ref) | 0.91 (0.41 to 2.00) | 0.50 (0.20 to 1.24) | 0.60 (0.22 to 1.64) | 0.16 |
| **Pooled (NHS+HPFS)** |  |  |  |  |  |
| Number of cases (N=179) | 46 | 49 | 54 | 30 |  |
| Age-adjusted\* | 1 (Ref) | 0.88 (0.59 to 1.32) | 0.68 (0.46 to 1.01) | 0.52 (0.33 to 0.84) | 0.003 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.87 (0.58 to 1.31) | 0.69 (0.46 to 1.04) | 0.55 (0.34 to 0.90) | 0.008 |
| Multivariable-adjusted¶ | 1 (Ref) | 0.88 (0.58 to 1.32) | 0.70 (0.46 to 1.05) | 0.56 (0.35 to 0.91) | 0.01 |

CI, confidence interval; HR, hazard ratio; Ref, reference group.

\*Adjusted for age (in months) and study period (two-year interval).

**\*\***Adjusted for age (in months), study period (two-year interval), gender (women, men), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current), body mass index (kg/m2, continuous), aspirin use (yes, no), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).

**¶**Multivariable-adjusted model\*\*+ type 2 diabetes (yes, no).

**Supplementary Table 5. Stratified analyses of** **dietary diabetes risk reduction score and** **risk of hepatocellular carcinoma in the pooled Nurses’ Health Study and Health Professionals Follow-up Study**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Dietary diabetes risk reduction score, HR (95% CI)** | | | | | | ***Ptrend*** | ***P*interaction** |
|  | Quartile 1 | Quartile 2 | | Quartile 3 | Quartile 4 |  |
| **Age, years** |  |  | |  |  |  |  |  |
| <65 (N=31) | 1 (Ref) | 1.04 (0.41 to 2.62) | | 0.61 (0.23 to 1.64) | 0.49 (0.14 to 1.70) |  | 0.16 | 0.88 |
| ≥65 (N=129) | 1 (Ref) | 0.77 (0.45 to 1.34) | | 0.80 (0.49 to 1.34) | 0.59 (0.33 to 1.03) |  | 0.08 |
| **BMI, kg/m2** |  |  | |  |  |  |  |  |
| <25 (N=48) | 1 (Ref) | 0.63 (0.26 to 1.55) | | 0.80 (0.37 to 1.75) | 0.48 (0.19 to 1.20) |  | 0.18 | 0.31 |
| ≥25 (N=112) | 1 (Ref) | 0.88 (0.50 to 1.54) | | 0.75 (0.43 to 1.30) | 0.66 (0.36 to 1.22) |  | 0.15 |
| **Smoking status** |  |  | |  |  |  |  |  |
| Never(N=73) | 1 (Ref) | 1.01 (0.53 to 1.94) | | 0.63 (0.33 to 1.23) | 0.65 (0.31 to 1.34) |  | 0.12 | 0.88 |
| Ever (N=87) | 1 (Ref) | 0.68 (0.34 to 1.37) | | 0.85 (0.46 to 1.58) | 0.52 (0.26 to 1.05) |  | 0.12 |
| **Type 2 diabetes** |  |  | |  |  |  |  |  |
| No (N=130) | 1 (Ref) | 0.82 (0.49 to 1.38) | | 0.77 (0.47 to 1.25) | 0.48(0.27 to 0.85) |  | 0.01 | 0.13 |
| Yes (N=30) | 1 (Ref) | 0.81 (0.22 to 2.90) | | 0.84 (0.25 to 2.80) | 1.22(0.36 to 4.15) |  | 0.59 |
| **Alcohol,** **g/day** |  |  | |  |  |  |  |  |
| <10 (N=115) | 1 (Ref) | 1.04 (0.58 to 1.86) | | 0.91 (0.52 to 1.60) | 0.95 (0.52 to 1.73) |  | 0.76 | 0.002 |
| ≥10 (N=45) | 1 (Ref) | 0.49 (0.21 to 1.14) | | 0.48 (0.23 to 1.02) | 0.13 (0.04 to 0.42) |  | 0.001 |
| **Physical activity, METS-hours/week** | | | |  |  |  |  |  |
| <9 (N=61) | 1 (Ref) | 1.34 (0.63 to 2.82) | | 1.15 (0.55 to 2.40) | 0.99 (0.41 to 2.39) |  | 0.87 | 0.09 |
| ≥9 (N=99) | 1 (Ref) | 0.58 (0.31 to 1.08) | | 0.57 (0.32 to 0.99) | 0.42 (0.23 to 0.78) |  | 0.01 |
| **Aspirin use** | | |  |  |  |  |  |  |
| No (N=107) | 1 (Ref) | 0.80 (0.45 to 1.43) | | 0.86 (0.50 to 1.47) | 0.60 (0.32 to 1.12) |  | 0.14 | 0.64 |
| Yes (N=53) | 1 (Ref) | 0.93 (0.40 to 2.12) | | 0.67 (0.30 to 1.50) | 0.55 (0.23 to 1.34) |  | 0.12 |

Adjusted for age (in months), gender (women, men), race (White, non-White), physical activity (METS-hours/week, continuous), body mass index (kg/m2, continuous), smoking status (never, past, current), aspirin use (no, yes), total alcohol intake (g/day, continuous), total coffee intake (≤1-2-3, ≥4 cups/day), and total calorie intake (kcal/day, tertiles). Notably, variables examined in this table were not adjusted for.

**Supplementary Table 6. Sensitivity analyses on dietary diabetes risk reduction score and risk of hepatocellular carcinoma** **according to HBV/HCV infections status.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Dietary diabetes risk reduction score, HR (95% CI)** | | | | ***P*trend** |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **HCC excluded HBV/HCV** |  |  |  |  |  |
| Number of cases (N=134) | 28 | 31 | 45 | 30 |  |
| Age-adjusted\* | 1 (Ref) | 0.79 (0.47 to 1.32) | 0.72 (0.44 to 1.16) | 0.55 (0.33 to 0.94) | 0.03 |
| Multivariable-adjusted\*\* | 1 (Ref) | 0.78 (0.46 to 1.31) | 0.73 (0.45 to 1.19) | 0.58 (0.33 to 1.00) | 0.05 |

CI, confidence interval; HR, hazard ratio; Ref, reference group.

\*Adjusted for age (in months) and study period (two-year interval).

**\*\***Adjusted for age (in months), study period (two-year interval), gender (women, men), race (White, non-White), physical activity (3, 3-<27, ≥27 METS-hours/week), smoking status (never, past, current), body mass index (kg/m2, continuous), aspirin use (yes, no), alcohol intake (g/day, continuous), and total calorie intake (kcal/day, tertiles).