**Associations of Saccharin Intake with All-cause, Cardiovascular and Cancer Mortality Risk in US adults**

Supplementary Tables

Table S1. χ2 test for the distribution of saccharin intake and abnormal glucose metabolism in the whole population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Saccharin intake (yes/no) | |  |
|  |  | 0 | 1 | Total |
| Diabetes and prediabetes (yes/no) | 0 | 8471 | 631 | 9102 |
| 1 | 6640 | 936 | 7576 |
|  | Total | 15111 | 1567 | 16678 |

χ2=142.797，ν=1，*P*<0.001

Table S2. χ2 test for the distribution of saccharin intake and overweight in the whole population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Saccharin intake (yes/no) | |  |
|  |  | 0 | 1 | Total |
| Overweight  (yes/no) | 0 | 6308 | 476 | 6784 |
| 1 | 8803 | 1091 | 9894 |
|  | Total | 15111 | 1567 | 16678 |

χ2=76.034，ν=1，*P*<0.001

Table S3. Distribution of health-related risk factors of the 936 people from the NHANES Ⅲ according to the absolute intake of saccharin a in diabetic and pre-diabetic population

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Quartiles of absolute saccharin intake (mg/d) | | | | *Pb* |
| 1 (<35.30) | 2 (35.30-70.49) | 3 (70.50-105.80) | 4 (>105.80) |
| All participants, No. | 344 | 262 | 130 | 200 |  |
| Continuous variables |  |  |  |  |  |
| Fasting glucose, mg/dL | 124.67(113.86-135.48) | 125.81(114.56-137.05) | 115.16(106.29-124.04) | 130.22(113.32-147.11) | 0.371 |
| Fasting insulin, μU/mL | 23.98(13.70-34.27) | 20.82(15.66-25.97) | 18.35(13.57-23.12) | 17.62(14.64-20.61) | 0.405 |
| HbA1C, % | 6.35(6.05-6.65) | 6.08(5.73-6.42) | 6.06(5.76-6.36) | 6.32(6.01-6.63) | 0.348 |
| C-peptide, pmol/mL | 0.95(0.86-1.04) | 1.04(0.92-1.16) | 0.96(0.78-1.14) | 1.01(0.89-1.12) | 0.659 |
| HOMA-IR | 11.59(1.56-21.63) | 7.47(4.98-9.96) | 6.51(3.63-9.39) | 6.48(4.60-8.36) | 0.527 |
| Triglycerides, mg/dL | 173.65(159.29-188.00) | 215.55(176.32-254.78) | 221.44(182.83-260.04) | 234.28(155.34-313.23) | 0.038\* |
| HDL, mg/dL | 48.79(46.31-51.26) | 48.09(45.95-50.24) | 46.59(43.53-49.64) | 46.34(43.98-48.71) | 0.358 |
| LDL, mg/dL | 143.65(137.55-149.75) | 133.51(123.80-143.22) | 132.98(114.48-151.49) | 133.01(125.28-140.75) | 0.258 |
| Waist circumference, cm | 99.37(97.14-101.59) | 102.20(99.91-104.48) | 100.38(95.50-105.27) | 100.78(98.15-103.41) | 0.465 |
| Systolic blood pressure, mm Hg | 130.53(128.28-132.78) | 130.74(128.50-132.98) | 133.35(129.43-137.27) | 135.90(132.35-139.45) | 0.032\* |
| Diastolic blood pressure, mm Hg | 75.22(73.80-76.64) | 76.20(74.62-77.77) | 78.11(75.58-80.64) | 76.14(74.02-78.27) | 0.244 |
| CRP, mg/dL | 0.53(0.40-0.66) | 0.47(0.37-0.57) | 0.56(0.33-0.78) | 0.51(0.43-0.58) | 0.790 |
| ALT, U/L | 18.18(16.26-20.10) | 18.72(16.25-21.20) | 18.11(15.20-21.02) | 17.25(14.99-19.52) | 0.855 |
| AST, U/L | 21.70(20.00-23.39) | 21.45(19.49-23.41) | 21.64(19.65-23.63) | 20.02(18.69-21.35) | 0.486 |
| AST : ALT ratio | 1.34(1.25-1.42) | 1.40(1.27-1.53) | 1.39(1.28-1.49) | 1.36(1.28-1.45) | 0.776 |
| Liver fat percentage, % | 2.06(1.71-2.41) | 2.24(1.83-2.65) | 2.29(1.65-2.93) | 2.15(1.68-2.63) | 0.884 |
| Liver fat score | 17.71(12.67-22.76) | 17.28(14.00-20.57) | 17.62(12.16-23.07) | 15.39(12.69-18.08) | 0.694 |
| Binary variables d |  |  |  |  |  |
| Hypertriglyceridemia, No.(%) | 24.0(18.9-30.1) | 35.2(26.4-45.0) | 43.9(31.1-57.5) | 31.0(22.4-41.2) | 0.027\* |
| Hypertension, No.(%) | 59.9(50.8-68.3) | 52.7(42.0-63.2) | 63.9(51.1-75.0) | 64.5(55.9-72.3) | 0.305 |
| Obesity, No.(%) | 35.1(26.7-44.6) | 43.3(35.2-51.7) | 37.2(25.7-50.4) | 38.5(28.9-49.1) | 0.573 |
| Elevated ALT, No.(%) | 31.7(22.0-43.3) | 37.0(26.9-48.3) | 28.3(16.7-43.9) | 34.1(23.1-47.1) | 0.805 |
| Elevated AST:ALT ratio, No.(%) | 11.1(7.1-17.0) | 16.5(10.9-24.4) | 10.4(5.4-18.9) | 11.4(6.3-19.7) | 0.377 |

a Values are weighted means(95%CI) or weighted percentages(95%CI). HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein;

b P value was assessed with General linear models adjusting for age and sex (continuous variables) or χ2 test (bivariate relationships).

d The following definitions were used for the binary variables: hypertriglyceridemia, triglycerides≥200mg/dL; obesity, BMI≥30.0; elevated ALT, ALT≥19.0 U/L; elevated AST:ALT ratio, ratio ≥2; elevated liver fat score, >−0.640.

All data analyses conducted in the table with sample weights provided by NHANES.

Table S4—Baseline demographic and lifestyle characteristics of the 1091 people from the NHANES Ⅲ according to the absolute intake of saccharin a in overweight population

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Quartiles of absolute saccharin intake (mg/d) | | | | *Pb* |
| 1 (<35.30) | 2 (35.30-70.49) | 3 (70.50-105.80) | 4 (>105.80) |
| All participants, No. | 411 | 303 | 151 | 226 |  |
| Age at recruitment, y | 52.81(50.28-55.35) | 51.08(49.02-53.14) | 51.05(46.24-55.86) | 49.82(46.52-53.12) | 0.397 |
| BMI, kg/m2 | 30.24(29.65-30.83) | 30.83(30.12-31.55) | 30.40(28.97-31.84) | 30.97(29.54-32.40) | 0.389 |
| Women, No.(%) | 60.0(51.3-68.2) | 61.4(52.2-69.8) | 53.3(39.9-66.2) | 49.0(38.6-59.5) | 0.073 |
| Non-Hispanic White, No.% | 80.1(73.7-85.3) | 82.9(76.9-87.6) | 82.7(74.7-88.6) | 87.8(83.1-91.3) | 0.009\* |
| Current smoking, No.(%) | 28.2(19.6-38.8) | 37.1(26.3-49.3) | 50.3(32.3-68.3) | 46.3(33.2-60.0) | 0.009\* |
| Current alcohol drinking, No.(%) | 47.4(36.8-58.2) | 53.8(45.0-62.4) | 53.0(37.9-67.6) | 48.2(36.3-60.3) | 0.990 |
| Poverty Income Ratio, % | 3.38(3.07-3.69) | 3.51(3.23-3.79) | 3.32(2.89-3.76) | 3.01(2.68-3.34) | 0.315 |
| Regular exercise, No.(%) | 75.9(67.7-82.5) | 76.1(69.4-81.8) | 73.3(60.5-83.2) | 79(69.8-86.0) | 0.708 |
| Family history of diabetes, No.(%) | 53.0(45.3-60.6) | 51.0(41.6-60.3) | 46.1(34.4-58.2) | 51.1(41.1-61.1) | 0.705 |
| Health status by physician's impression |  |  |  |  | 0.163 |
| Excellent | 29.8(22.2-38.8) | 25.8(17.5-36.4) | 28.8(17.3-43.8) | 30.3(18.3-45.9) |  |
| Very good | 23.6(17.5-30.9) | 30.6(23.2-39.2) | 23.1(12.4-38.8) | 21.1(13.7-31.0) |  |
| Good | 32.6(24.6-41.7) | 30.3(21.4-41.1) | 32.4(21.1-46.1) | 28.0(18.4-40.2) |  |
| Fair | 9.9(6.4-15.0) | 10.6(6.5-16.7) | 10.9(6.6-17.3) | 11.6(6.3-20.4) |  |
| Poor | 2.3(1.0-5.1) | 0.8(0.2-3.4) | 1.6(0.6-4.8) | 4.3(0.9-17.5) |  |
| Dietary consumption |  |  |  |  |  |
| Energy, kcal/d | 1904.77(1717.40-2092.15) | 1948.24(1801.47-2095.00) | 2161.98(1901.51-2422.46) | 2064.60(1893.89-2234.71) | 0.589 |
| Carbonhydrate, % of energy | 46.38(43.84-48.91) | 46.62(44.59-48.65) | 47.27(4502-49.51) | 47.29(45.09-49.49) | 0.881 |
| SFAs, % of energy | 11.96(1.16-12.75) | 12.37(11.66-13.07) | 11.81(11.08-12.54) | 11.94(11.11-12.77) | 0.671 |
| MUFAs, % of energy | 13.93(13.11-14.75) | 14.25(13.43-15.08) | 14.08(13.32-14.85) | 13.94(13.03-14.84) | 0.888 |
| PUFAs, % of energy | 7.28(6.77-7.79) | 7.44(7.02-7.86) | 7.46(6.78-8.15) | 7.74(6.99-8.49) | 0.865 |
| Animal protein, % of energy | 11.20(10.47-11.94) | 11.11(10.28-11.94) | 10.80(9.80-11.80) | 11.13(10.19-12.07) | 0.937 |
| Vegetable protein, % of energy | 4.98(4.58-5.39) | 4.85(4.54-5.16) | 4.98(4.94-5.41) | 5.00(4.64-5.36) | 0.807 |
| Total sugars, g/d | 93.07(82.06-104.08) | 95.79(86.34-105.23) | 103.41(78.94-127.89) | 92.13(79.08-105.19) | 0.663 |
| Fiber, g/d | 17.01(15.57-18.45) | 16.32(15.21-17.43) | 17.95(15.50-20.40) | 18.58(16.77-20.40) | 0.240 |
| Alcohol, % of energy | 1.72(0.78-2.66) | 1.78(1.00-2.55) | 1.74(0.53-2.95) | 1.27(0.61-1.94) | 0.510 |
| Healthy Eating Index (HEI) | 64.44(61.71-67.16) | 63.80(61.35-66.25) | 64.63(62.11-67.14) | 36.13(61.02-65.24) | 0.870 |

a Values are weighted means(95%CI) or weighted percentages(95%CI).

b P value was assessed with General linear models adjusting for age and sex (continuous variables) or χ2 test (bivariate relationships).

All data analyses conducted in the table with sample weights provided by NHANES.

Table S5—Distribution of health-related risk factors of the 1091 people from the NHANES Ⅲ according to the absolute intake of saccharin a in overweight population

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Quartiles of absolute saccharin intake (mg/d) | | | | *Pb* |
| 1 (<35.30) | 2 (35.30-70.49) | 3 (70.50-105.80) | 4 (>105.80) |
| All participants, No. | 411 | 303 | 151 | 226 |  |
| Continuous variables |  |  |  |  |  |
| Fasting glucose, mg/dL | 110.32(102.90-117.74) | 111.81(105.43-118.19) | 103.93(97.03-110.84) | 107.70(100.67-114.73) | 0.489 |
| Fasting insulin, uU/mL | 16.50(12.81-20.19) | 15.97(14.25-17.70) | 15.20(11.81-18.59) | 17.16(14.69-19.64) | 0.819 |
| HbA1C, % | 5.76(5.56-5.95) | 5.66(5.46-5.86) | 5.65(5.40-5.91) | 5.72(5.52-5.90) | 0.810 |
| C-peptide, pmol/mL | 0.90(0.82-0.99) | 0.95(0.84-1.05) | 0.88(0.76-1.00) | 1.06(0.94-1.19) | 0.032\* |
| HOMA-IR | 5.13(3.69-6.57) | 5.11(4.17-6.05) | 4.82(2.96-6.68) | 5.24(4.09-6.40) | 0.764 |
| Triglycerides, mg/dL | 160.69(146.25-175.14) | 196.57(167.73-225.42) | 171.97(148.06-195.88) | 225.29(157.47-293.12) | 0.001\* |
| HDL, mg/dL | 49.22(46.78-51.67) | 47.76(45.18-50.34) | 45.48(42.70-48.26) | 45.50(43.47-47.54) | 0.037\* |
| LDL, mg/dL | 138.29(134.89-141.69) | 135.14(132.41-137.87) | 134.62(128.35-140.89) | 135.41(132.59-138.23) | 0.158 |
| Waist circumference, cm | 101.00(99.29-102.71) | 102.47(100.38-104.56) | 101.34(96.75-105.92) | 103.31(100.02-106.59) | 0.299 |
| Systolic blood pressure, mm Hg | 127.52(124.77-130.26) | 129.20(121.10-137.31) | 128.40(124.41-132.38) | 128.97(124.71-133.23) | 0.123 |
| Diastolic blood pressure, mm Hg | 75.99(74.88-77.11) | 79.14(71.43-86.85) | 77.36(74.91-79.80) | 75.56(73.67-77.46) | 0.598 |
| CRP, mg/dL | 0.52(0.40-0.64) | 0.47(0.40-0.53) | 0.47(0.31-0.63) | 0.51(0.42-0.60) | 0.726 |
| ALT, U/L | 17.70(16.06-19.34) | 18.39(16.16-20.61) | 18.54915.30-21.78） | 18.46(16.49-20.43) | 0.782 |
| AST, U/L | 21.87(20.39-23.34) | 20.61(19.05-22.17) | 21.47（19.58-23.36） | 20.72(19.53-21.91) | 0.079 |
| AST : ALT ratio | 1.37(1.30-1.45) | 1.31(1.22-1.41) | 1.37(1.27-1.47) | 1.29(1.19-1.35) | 0.814 |
| Liver fat percentage, % | 4.93(4.20-5.65) | 5.01(4.45-5.59) | 4.84(3.87-5.82) | 5.29(4.39-6.19) | 0.804 |
| Liver fat score | 13.96(10.25-17.67) | 13.47(11.72-15.23) | 12.73(9.16-16.29) | 14.69(12.07-17.31) | 0.578 |
| Binary variablesd |  |  |  |  |  |
| Hypertriglyceridemia, No.(%) | 20.1(15.2-26.0) | 27.4(20.6-35.5) | 29.3(18.9-42.3) | 30.8(23.9-38.7) | 0.005\* |
| Hypertension, No.(%) | 47.7(40.2-55.3) | 36.5(30.1-43.5) | 40.5(29.4-52.6) | 48.8(39.4-58.3) | 0.292 |
| Obesity, No.(%) | 42.6(34.5-51.1) | 52.4(44.4-60.4) | 41.6(29.1-55.1) | 45.3(34.4-56.7) | 0.803 |
| Elevated ALT, No.(%) | 33.2(24.3-43.5) | 34.4(25.6-44.4) | 31.3(19.7-45.8) | 37.8(28.1-48.6) | 0.785 |
| Elevated AST: ALT ratio, No.(%) | 12.1(7.8-18.4) | 11.6(8.1-16.2) | 13.8(7.6-23.7) | 11.9(6.6-20.5) | 0.568 |

a Values are weighted means(95%CI) or weighted percentages(95%CI). HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein;

b P value was assessed with General linear models adjusting for age and sex (continuous variables) or χ2 test (bivariate relationships).

d The following definitions were used for the binary variables: hypertension, systolic blood pressure ≥130 mm Hg and (or) diastolic blood pressure ≥80 mm Hg; hypertriglyceridemia, triglycerides≥200mg/dL; obesity, BMI≥30.0; elevated ALT, ALT≥19.0 U/L; elevated AST:ALT ratio, ratio ≥2.

All data analyses conducted in the table with sample weights provided by NHANES.

Table S6— Associations of absolute saccharin intake with all-cause, cardiovascular and cancer mortality in NHANES Ⅲa in overweight population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Quartiles of absolute saccharin intake (mg/d) | | | | *P-trendb* | Proportional hazard assumption *P*c |
| 1 (<35.30) | 2 (35.30-70.50) | 3 (70.49-105.80) | 4 (>105.80) |
| All-cause mortality |  |  |  |  |  | 0.712 |
| Death/Person-months | 225/83,876 | 164/62,772 | 89/31,045 | 125/45,979 |  |  |
| Unadjusted | 1(ref) | 0.979(0.666-1.439) | 0.911(0.588-1.411) | 1.190(0.831-1.706) | 0.509 |  |
| Model 1 | 1(ref) | 1.070(0.724-1.582) | 0.948(0.673-1.336) | 1.371(0.997-1.885) | 0.122 |  |
| Model 2 | 1(ref) | 1.257(0.690-2.291) | 0.931(0.582-1.489) | 2.122(1.278-3.523) | 0.022\* |  |
| Model 3 | 1(ref) | 1.295(0.676-2.480) | 1.037(0.550-1.956) | 2.087(1.054-4.133) | 0.094 |  |
| Model 4 | 1(ref) | 1.293(0.677-2.469) | 1.025(0.552-1.904) | 2.072(1.069-4.018) | 0.09 |  |
| CVD mortality |  |  |  |  |  | 0.334 |
| Death/Person-months | 83/83,876 | 53/62,772 | 35/31,045 | 55/45,979 |  |  |
| Unadjusted | 1(ref) | 0.765(0.444-1.319) | 0.714(0.356-1.430) | 1.564(0.945-2.588) | 0.231 |  |
| Model 1 | 1(ref) | 0.790(0.336-1.855) | 0.198(0.065-0.603) | 2.035(1.046-3.959) | 0.091 |  |
| Model 2 | 1(ref) | 0.716(0.286-1.795) | 0.167(0.056-0.503) | 1.929(0.724-5.136) | 0.453 |  |
| Model 3 | 1(ref) | 0.786(0.315-1.964) | 0.122(0.035-.422) | 1.618(0.427-6.126) | 0.949 |  |
| Model 4 | 1(ref) | 0.784(0.305-2.014) | 0.123(0.035-0.428) | 1.637(0.454-5.896) | 0.942 |  |
| Cancer mortality |  |  |  |  |  | 0.824 |
| Death/Person-months | 35/83,876 | 26/49,416 | 14/31,045 | 23/45,979 |  |  |
| Unadjusted | 1(ref) | 1.319(0.547-3.184) | 1.149(0.546-2.420) | 1.641(0.813-3.312) | 0.165 |  |
| Model 1 | 1(ref) | 1.384(0.589-3.254) | 1.207(0.595-2.450) | 1.842(0.899-3.774) | 0.100 |  |
| Model 2 | 1(ref) | 3.366(1.056-10.728) | 2.322(0.958-5.632) | 5.194(2.001-13.481) | 0.001\* |  |
| Model 3 | 1(ref) | 3.222(0.875-11.860) | 4.018(1.185-13.631) | 5.924(1.799-19.503) | 0.001\* |  |
| Model 4 | 1(ref) | 3.370(0.861-13.194) | 3.983(1.123-14.131) | 5.897(1.777-19.568) | 0.001\* |  |

a Values are n or weighted HR(95%CI). CVD: cardiovascular disease

Model 1: adjusted for age, sex, and race. Model 2: further adjusted BMI, family poverty income ratio, current smoking, current drinking, regular exercise, family history of diabetes, health status and dietary consumption including energy (kcal/d), carbohydrate (%), SFAs (%), MUFAs (%), PUFAs (%), animal protein (%), vegetable protein (%), fiber (g/d), alcohol (%) and HEI score. Model 3: further adjusted CVD risk factors including fasting glucose, HbA1c, serum cholesterol, Serum triglycerides, serum HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein and AST/ALT. Model 4: further adjusted another widely used NNS aspartame (mg/d).

b *P-trend* was calculated by median within each group.

c Proportional hazard assumption *P* for saccharin intakewas calculated by conducting Kaplen-Meier test.

Table S7— Associations of saccharin intake per weight with all-cause, cardiovascular and cancer mortality in NHANES Ⅲa in overweight population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Quartiles of saccharin intake per weight (mg/kg·d) | | | | *P-trendb* | Proportional hazard assumption *P*c |
| 1 (<0.42) | 2 (0.42-0.76) | 3 (0.77-1.25) | 4 (>1.25) |
| All-cause mortality |  |  |  |  |  | 0.603 |
| Death/Person-months | 139/58,180 | 161/54,978 | 146/56,276 | 157/54,236 |  |  |
| Unadjusted | 1(ref) | 1.175(0.775-1.781) | 0.955(0.667-1.368) | 1.256(0.870-1.813) | 0.277 |  |
| Model 1 | 1(ref) | 1.170(0.810-1.690) | 1.011(0.687-1.488) | 1.354(0.952-1.926) | 0.098 |  |
| Model 2 | 1(ref) | 1.221(0.771-1.935) | 0.958(0.461-1.989) | 2.189(1.335-3.589) | 0.003\* |  |
| Model 3 | 1(ref) | 1.314(0.838-2.058) | 0.925(0.447-1.914) | 2.174(1.174-4.028) | 0.024\* |  |
| Model 4 | 1(ref) | 1.314(0.838-2.060) | 0.929(0.441-1.956) | 2.165(1.194-3.928) | 0.022\* |  |
| CVD mortality |  |  |  |  |  | 0.405 |
| Death/Person-months | 49/58,180 | 56/54,978 | 52/56,276 | 69/54,236 |  |  |
| Unadjusted | 1(ref) | 1.092(0.553-2.156) | 0.816(0.434-1.534) | 1.628(0.967-2.741) | 0.028\* |  |
| Model 1 | 1(ref) | 1.039(0.538-2.005) | 0.851(0.439-1.649) | 1.686(1.016-2.795) | 0.011\* |  |
| Model 2 | 1(ref) | 0.727(0.356-1.483) | 0.482(0.152-1.529) | 1.795(0.721-4.469) | 0.137 |  |
| Model 3 | 1(ref) | 0.688(0.324-1.463) | 0.444(0.129-1.524) | 1.385(0.410-4.675) | 0.641 |  |
| Model 4 | 1(ref) | 0.663(0.297-1.481) | 0.426(0.116-1.558) | 1.404(0.438-4.503) | 0.621 |  |
| Cancer mortality |  |  |  |  |  | 0.986 |
| Death/Person-months | 27/58,180 | 24/54,978 | 14/56,276 | 33/54,236 |  |  |
| Unadjusted | 1(ref) | 1.021(0.463-2.249) | 0.855(0.367-1.995) | 1.637(0.867-3.089) | 0.084 |  |
| Model 1 | 1(ref) | 0.976(0.459-2.078) | 0.879(0.370-2.086) | 1.724(0.897-3.313) | 0.050\* |  |
| Model 2 | 1(ref) | 2.941(0.767-11.275) | 2.588(0.655-10.225) | 5.702(2.119-15.345) | 0.003\* |  |
| Model 3 | 1(ref) | 2.818(0.897-8.851) | 2.871(0.666-2.372) | 7.380(2.144-25.405) | <0.001\* |  |
| Model 4 | 1(ref) | 2.876(0.883-9.365) | 3.125(0.669-14.595) | 7.369(2.122-25.592) | <0.001\* |  |

a Values are n or weighted HR(95%CI). CVD: cardiovascular disease

Model 1: adjusted for age, sex, and race. Model 2: further adjusted BMI, family poverty income ratio, current smoking, current drinking, regular exercise, family history of diabetes, health status and dietary consumption including energy(kcal/d), carbohydrate(%), SFAs(%), MUFAs(%), PUFAs(%), animal protein(%), vegetable protein(%), fiber(g/d), alcohol(%) and HEI score. Model 3: further adjusted CVD risk factors including fasting glucose, HbA1c, serum cholesterol, Serum triglycerides, serum HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein and AST/ALT. Model 4: further adjusted another widely used NNS aspartame (mg/d).

b *P*-trend was calculated by median within each group.

c Proportional hazard assumption *P* for saccharin intake was calculated by conducting Kaplen-Meier test.

Table S8. Associations of absolute saccharin intake with all-cause, cardiovascular and cancer mortality after excluding participants who died prematurely in NHANES Ⅲ a in diabetic and pre-diabetic population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Quartiles of absolute saccharin intake (mg/d) | | | | *P-trendb* | Proportional hazard assumption *P*c |
| 1 (<35.30) | 2 (35.30-70.49) | 3 (70.50-105.80) | 4 (>105.80) |
| All-cause mortality |  |  |  |  |  | 0.622 |
| Death/Person-months | 184/63,056 | 131/48,003 | 73/24,879 | 113/33,991 |  |  |
| Unadjusted | 1(ref) | 0.98(0.62-1.55) | 0.98(0.62-1.54) | 1.31(0.85-2.00) | 0.180 |  |
| Model 1 | 1(ref) | 1.03(0.70-1.51) | 0.96(0.66-1.40) | 1.31(1.00-1.72) | 0.066 |  |
| Model 2 | 1(ref) | 1.10(0.72-1.66) | 1.02(0.70-1.48) | 1.40(1.06-1.85) | 0.020\* |  |
| Model 3 | 1(ref) | 0.99(0.71-1.38) | 0.98(0.66-1.45) | 1.41(1.05-1.89) | 0.026\* |  |
| Model 4 | 1(ref) | 0.98(0.70-1.37) | 0.98(0.66-1.46) | 1.41(1.05-1.90) | 0.025\* |  |
| CVD mortality |  |  |  |  |  | 0.476 |
| Death/Person-months | 64/63,056 | 35/48,003 | 22/24,879 | 49/33,991 |  |  |
| Unadjusted | 1(ref) | 0.65(0.33-1.28) | 0.69(0.27-1.73) | 1.86(1.08-3.20) | 0.019\* |  |
| Model 1 | 1(ref) | 0.66(0.32-1.38) | 0.64(0.26-1.59) | 1.88(1.23-2.87) | 0.005\* |  |
| Model 2 | 1(ref) | 0.70(0.34-1.42) | 0.64(0.25-1.68) | 1.98(1.19-3.29) | 0.007\* |  |
| Model 3 | 1(ref) | 0.72(0.37-1.39) | 0.63(0.27-1.46) | 1.90(1.09-3.32) | 0.021\* |  |
| Model 4 | 1(ref) | 0.75(0.39-1.43) | 0.62(0.26-1.48) | 1.88(1.06-3.31) | 0.026\* |  |
| Cancer mortality |  |  |  |  |  | 0.171 |
| Death/Person-months | 28/63,056 | 18/48,003 | 12/24,879 | 22/33,991 |  |  |
| Unadjusted | 1(ref) | 1.75(0.73-4.21) | 1.85(0.92-3.73) | 2.63(1.25-5.54) | 0.006\* |  |
| Model 1 | 1(ref) | 1.74(0.74-4.10) | 1.74(0.87-3.50) | 2.74(1.35-5.55) | 0.002\* |  |
| Model 2 | 1(ref) | 2.04(0.72-5.79) | 2.00(0.88-4.55) | 2.85(1.25-6.53) | 0.008\* |  |
| Model 3 | 1(ref) | 0.98(0.35-2.75) | 1.46(0.59-3.62) | 2.75(1.36-5.58) | 0.001\* |  |
| Model 4 | 1(ref) | 0.97(0.34-2.76) | 1.47(0.58-3.73) | 2.65(1.18-5.92) | 0.007\* |  |

a Values are n or weighted HR (95%CI). CVD: cardiovascular disease

Model 1: adjusted for age, sex, and race. Model 2: further adjusted BMI, family poverty income ratio, current smoking, current drinking, regular exercise, family history of diabetes, health status and dietary consumption including energy(kcal/d), carbohydrate (%), SFAs (%), MUFAs (%), MUFAs (%), animal protein (%), vegetable protein (%), fiber(g/d), alcohol (%) and HEI score. Model 3: further adjusted CVD risk factors including fasting glucose, HbA1c, serum cholesterol, Serum triglycerides, serum HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein and AST/ALT. Model 4: further adjusted another widely used NNS aspartame (mg/d).

b P-trend was calculated by median within each group.

c Proportional hazard assumption P for saccharin intake was calculated by conducting Kaplen-Meier test.

Table S9. Associations of saccharin intake per weight with all-cause, cardiovascular and cancer mortality after excluding participants who died prematurely in NHANES Ⅲ a in diabetic and pre-diabetic population

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Quartiles of saccharin intake per weight (mg/kg·d) | | | | *P-trendb* | Proportional hazard  assumption *P*c |  |
| 1 (<0.46) | 2 (0.46-0.81) | 3 (0.82-1.36) | 4 (>1.36) |  |
| All-cause mortality |  |  |  |  |  | 0.827 |  |
| Death/Person-months | 130/45,584 | 117/42,578 | 123/42,805 | 131/38,962 |  |  |  |
| Unadjusted | 1(ref) | 0.93(0.57-1.52) | 0.91(0.59-1.42) | 1.24(0.80-1.93) | 0.182 |  |  |
| Model 1 | 1(ref) | 1.08(0.71-1.64) | 0.94(0.63-1.40) | 1.20(0.84-1.71) | 0.322 |  |  |
| Model 2 | 1(ref) | 1.17(0.73-1.89) | 1.05(0.66-1.68) | 1.36(0.94-1.97) | 0.082 |  |  |
| Model 3 | 1(ref) | 0.99(0.69-1.40) | 0.92(0.60-1.42) | 1.36(0.99-1.87) | 0.027\* |  |  |
| Model 4 | 1(ref) | 0.98(0.68-1.41) | 0.92(0.60-1.43) | 1.36(0.99-1.87) | 0.027\* |  |  |
| CVD mortality |  |  |  |  |  | 0.649 |  |
| Death/Person-months | 44/45,584 | 38/42,578 | 36/42,805 | 52/38,962 |  |  |  |
| Unadjusted | 1(ref) | 0.90(0.40-2.04) | 0.73(0.32-1.66) | 1.78(0.95-3.31) | 0.018\* |  |  |
| Model 1 | 1(ref) | 1.06(0.47-2.38) | 0.77(0.36-1.67) | 1.73(1.00-2.98) | 0.023\* |  |  |
| Model 2 | 1(ref) | 1.17(0.53-2.55) | 0.90(0.40-2.03) | 1.98(1.02-3.84) | 0.027\* |  |  |
| Model 3 | 1(ref) | 1.12(0.51-2.42) | 0.83(0.39-1.79) | 1.92(0.96-3.85) | 0.034\* |  |  |
| Model 4 | 1(ref) | 1.18(0.54-2.57) | 0.81(0.37-1.78) | 1.91(0.95-3.85) | 0.037\* |  |  |
| Cancer mortality |  |  |  |  |  | 0.223 |  |
| Death/Person-months | 21/45,584 | 19/42,578 | 13/42,805 | 27/38,962 |  |  |  |
| Unadjusted | 1(ref) | 1.35(0.58-3.16) | 1.02(0.49-2.12) | 2.19(1.13-4.27) | 0.026\* |  |  |
| Model 1 | 1(ref) | 1.45(0.66-3.20) | 1.01(0.49-2.08) | 2.13(1.13-4.01) | 0.035\* |  |  |
| Model 2 | 1(ref) | 1.74(0.63-4.80) | 1.02(0.45-2.28) | 2.71(1.16-6.35) | 0.026\* |  |  |
| Model 3 | 1(ref) | 0.87(0.36-2.13) | 0.72(0.28-1.87) | 2.40(1.27-4.53) | 0.001\* |  |  |
| Model 4 | 1(ref) | 0.84(0.35-1.99) | 0.73(0.28-1.90) | 2.30(1.16-4.57) | 0.005\* |  |  |

a Values are n or weighted HR (95%CI). CVD: cardiovascular disease

Model 1: adjusted for age, sex, and race. Model 2: further adjusted BMI, family poverty income ratio, current smoking, current drinking, regular exercise, family history of diabetes, health status and dietary consumption including energy(kcal/d), carbon hydrate (%), SFAs (%), MUFAs (%), MUFAs (%), animal protein (%), vegetable protein (%), fiber (g/d), alcohol (%) and HEI score. Model 3: further adjusted CVD risk factors including fasting glucose, HbA1c, serum cholesterol, Serum triglycerides, serum HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein and AST/ALT. Model 4: further adjusted another widely used NNS aspartame (mg/d).

b P-trend was calculated by median within each group.

c Proportional hazard assumption P for saccharin intake was calculated by conducting Kaplen-Meier test.

**Supplementary Figure**

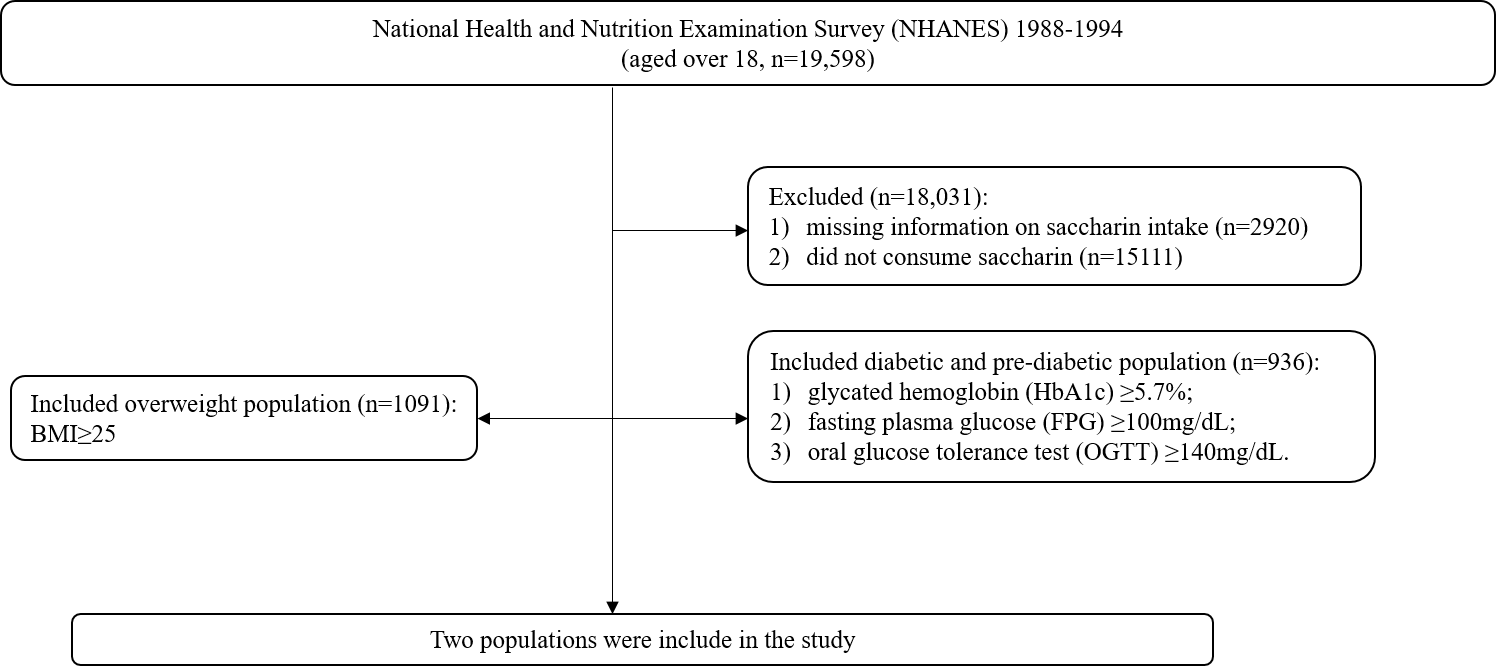
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Figure S1. Flow chart of study design.



Figure S2. Multivariable adjusted HRs for all-cause, CVD, and cancer mortality in pre-diabetic and diabetic population. Model 1: adjusted for age, sex, and race. Model 2: further adjusted BMI, family poverty income ratio, current smoking, current drinking, regular exercise, family history of diabetes, health status and dietary consumption including energy (kcal/d), carbohydrate (%), SFAs (%), MUFAs (%), MUFAs (%), animal protein (%), vegetable protein (%), fiber (g/d), alcohol (%) and HEI score. Model 3: further adjusted CVD risk factors including fasting glucose, HbA1c, serum cholesterol, Serum triglycerides, serum HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein and AST/ALT. Model 4: further adjusted another widely used NNS aspartame (mg/d).



Figure S3. Multivariable adjusted HRs for association between relative saccharin intake and all-cause, CVD, and cancer mortality stratified by sex, total sugar intake and glycated hemoglobin levels, respectively. The models were adjusted by using covariates in model 3.