**Irritable bowel syndrome and long-term risk of cancer: a prospective cohort study among 0.5 million adults in UK Biobank**

**Supplementary file**

**Table S1.** **ICD codes and Field ID defining irritable bowel syndrome (IBS) in UKB.**

|  |  |  |
| --- | --- | --- |
| **Disease** | **ICD-10** | **Data field ID in UKB** |
| IBS | K58 | 131638 |

Note: IBS: irritable bowel syndrome; ICD: international classification disease.

**Table S2.** **ICD codes used to define different cancers in the study.**

|  |  |  |
| --- | --- | --- |
| **Type of cancer** | **Category** | **ICD-10** |
| Digestive cancers | Colon cancer | C18 (C18.0-C18.9) |
|  | Rectal cancer | C20 |
|  | Liver & Biliary tract cancer | C22 (C22.0-C22.9), C23, C24 (C24.0-C24.9) |
|  | Esophagus cancer | C15 (C15.0-C15.9) |
|  | Stomach cancer | C16 (C16.0-C16.9) |
|  | Other digestive cancers | C17 (C17.0-C17.9), C19, C21 (C21.0-C21.8), C25 (C25.0-C25.9), C26 (C26.0-C26.9) |
| Breast cancer |  | C50 (C50.0-C50.9) |
| Genital cancer, female |  | C51 (C51.0-C51.9), C52, C53 (C53.0-C53.9), C54 (C54.0-C54.9), C55, C56, C57 (C57.0-C57.9), C58 |
| Genital cancer, male |  | C60 (C61.0-C61.9), C61, C62 (C62.0-C62.9), C63 (C63.0-C63.2) |
| CNS cancer |  | C69 (C69.0-C69.9), C70 (C70.0-C70.9), C71 (C71.0-C71.9), C72 (C72.0-C72.9) |
| Thyroid & endocrine cancer |  | C73, C74 (C74.0-C74.9), C75 (C75.0-C75.5) |
| Skin cancer | Melanoma | C43 (C43.0-C43.9) |
|  | Non-melanoma | C44 (C44.0-C44.9) |
| Urinary tract cancer |  | C64, C65, C66, C67 (C67.0-C67.9), C68 (C68.0-C68.9) |
| Haematological cancer |  | C81 (C81.0-C81.9), C82 (C82.0-C82.9), C83 (C83.0-C83.9), C84(C84.0-C84.5), C85(C85.0-C85.9), C86, C88(C88.0-C88.9), C90(C90.0-C90.3), C91(C91.0-C91.9), C92(C92.0-C92.9), C93(C93.0-C93.1), C94(C94.0-C94.6), C95(C95.0-C95.9), C96(C96.1-C96.9) |

Note: CNS: central nervous system; ICD: international classification disease.

**Table S3.** **Absolute incidence rates per 1000 person years (95%CI) of overall cancer in patients with IBS and reference individuals.**

|  |  |  |
| --- | --- | --- |
|  | **IBS (N=22338)** | **Non-IBS (N=427257)** |
| No. of Cancers | 2937 | 60556 |
| Person years | 255939 | 4841051 |
| Incidence rate | 11.47(11.07-11.90) | 12.51(12.41-12.61) |
| **Gender** |  |  |
| **Male** |  |  |
| No. of Cancers | 908 | 32304 |
| Person years | 67682 | 2279210 |
| Incidence rate | 13.42(12.57-14.32) | 14.17(14.02-14.33) |
| **Female** |  |  |
| No. of Cancers | 2029 | 28252 |
| Person years | 188257 | 2561841 |
| Incidence rate | 10.78(10.32-11.26) | 11.03(10.90-11.16) |
| **Age** |  |  |
| **<45 years** |  |  |
| No. of Cancers | 137 | 2308 |
| Person years | 28950 | 563617 |
| Incidence rate | 4.73(4.00-5.59) | 4.09(3.93-4.27) |
| **45-59 years** |  |  |
| No. of Cancers | 1143 | 21160 |
| Person years | 130254 | 2366990 |
| Incidence rate | 8.78(8.28-9.30) | 8.94(8.82-9.06) |
| **≥60 years** |  |  |
| No. of Cancers | 1657 | 37088 |
| Person years | 96735 | 1910444 |
| Incidence rate | 17.13(16.32-17.97) | 19.41(19.22-19.61) |

Note: IBS: irritable bowel syndrome; CI: confidence interval.

**Table S4.** **Absolute cancer specific mortality per 1000 person years (95%CI) in patients with IBS and reference individuals.**

|  |  |  |
| --- | --- | --- |
|  | **IBS (N=22338)** | **Non-IBS (N=427257)** |
| No. of cancer specific deaths | 512 | 12282 |
| Person years | 255939 | 4841051 |
| Incidence rate | 2.00(1.83-2.18) | 2.54(2.49-2.58) |
| **Gender** |  |  |
| **Male** |  |  |
| No. of cancer specific deaths | 165 | 7065 |
| Person years | 72355 | 2440666 |
| Incidence rate | 2.28(1.96-2.66) | 2.89(2.83-2.96) |
| **Female** |  |  |
| No. of cancer specific deaths | 347 | 5217 |
| Person years | 199761 | 2720202 |
| Incidence rate | 1.74(1.56-1.93) | 1.92(1.87-1.97) |
| **Age** |  |  |
| **<45 years** |  |  |
| No. of cancer specific deaths | 10 | 248 |
| Person years | 29830 | 577297 |
| Incidence rate | 0.34(0.18-0.62) | 0.43(0.38-0.49) |
| **45-59 years** |  |  |
| No. of cancer specific deaths | 182 | 3564 |
| Person years | 136683 | 2484459 |
| Incidence rate | 1.33(1.15-1.54) | 1.43(1.39-1.48) |
| **≥60 years** |  |  |
| No. of cancer specific deaths | 320 | 8470 |
| Person years | 105603 | 2099112 |
| Incidence rate | 3.03(2.72-3.38) | 4.04(3.95-4.12) |

Note: IBS: irritable bowel syndrome; CI: confidence interval.

**Table S5.** **Absolute incidence rates per 1000 person years (95% confidence interval) of each site-specific cancer in patients with IBS and reference individuals.**

|  |  |  |
| --- | --- | --- |
|  | **IBS** | **Non-IBS** |
| N | 22338 | 427257 |
| Person years | 255939 | 4841051 |
| **Type of cancer** |  |  |
| Digestive |  |  |
| No. of cancers | 306 | 8104 |
| Incidence rate | 1.20(1.07-1.34) | 1.67(1.64-1.71) |
| Central Nervous system |  |  |
| No. of cancers | 41 | 776 |
| Incidence rate | 0.16(0.12-0.22) | 0.16(0.15-0.17) |
| Thyroid & other endocrine |  |  |
| No. of cancers | 20 | 371 |
| Incidence rate | 0.08(0.05-0.12) | 0.08(0.07-0.08) |
| Skin |  |  |
| No. of cancers | 972 | 20076 |
| Incidence rate | 3.80(3.57-4.04) | 4.15(4.09-4.20) |
| Melanoma |  |  |
| No. of cancers | 96 | 2324 |
| Incidence rate | 0.38(0.31-0.46) | 0.48(0.46-0.50) |
| Non-melanoma |  |  |
| No. of cancers | 885 | 18193 |
| Incidence rate | 3.46(3.24-3.69) | 3.76(3.70-3.81) |
| Urinary tract |  |  |
| No. of cancers | 98 | 2228 |
| Incidence rate | 0.38(0.31-0.47) | 0.46(0.44-0.48) |
| Haematological |  |  |
| No. of cancers | 167 | 3662 |
| Incidence rate | 0.65(0.56-0.76) | 0.76(0.73-0.78) |
| Breast\* |  |  |
| No. of cancers | 532 | 7223 |
| Person years | 188257 | 2561841 |
| Incidence rate | 2.83(2.60-3.08) | 2.82(2.76-2.89) |
| Genital, female\* | |  |
| No. of cancers | 134 | 2334 |
| Person years | 188257 | 2561841 |
| Incidence rate | 0.71(0.60-0.84) | 0.91(0.87-0.95) |
| Genital, male# |  |  |
| No. of cancers | 264 | 9290 |
| Person years | 67682 | 2279210 |
| Incidence rate | 3.90(3.46-4.40) | 4.08(3.99-4.16) |

Note: \*: incidence rate was calculated in female participants; #: incidence rate was calculated in male participants; IBS: irritable bowel syndrome.

**Figure S1. Cumulative incidence of each site-specific cancer in patients with IBS and reference individuals (estimated by Kaplan-Meier method). A. Digestive cancer; B. Central nervous system cancer; C. Thyroid and other endocrine cancer; D. Skin cancer; E. Melanoma; F. Non-melanoma; G.** **urinary tract cancer; H. Haematological cancer; I. Breast cancer; J. Female genital cancer; K. Male genital cancer.** IBS: irritable bowel syndrome.

**A. Digestive cancer**

****

**D. Skin cancer**

**C. Thyroid and other endocrine cancer**

**B. Central nervous system cancer**

****

****

**H. Haematological cancer**

**G. Urinary tract cancer**

**F. Non-melanoma**

**E. Melanoma**

****

****

**K. Male genital cancer**

**J. Female genital cancer**

**I. Breast cancer**

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**Table S6.** **Absolute incidence rates per 1000 person years (95% confidence interval) of each type of digestive cancers in patients with IBS and reference individuals.**

|  |  |  |
| --- | --- | --- |
|  | **IBS** | **Non-IBS** |
| N | 22338 | 427257 |
| Person years | 255939 | 4841051 |
| **Type of digestive cancers** | |  |
| Colorectal cancer |  |  |
| No. of cancers | 153 | 4395 |
| Incidence rate | 0.60(0.51-0.70) | 0.91(0.88-0.94) |
| Colon cancer |  |  |
| No. of cancers | 115 | 3117 |
| Incidence rate | 0.45(0.37-0.54) | 0.64(0.62-0.67) |
| Rectal cancer |  |  |
| No. of cancers | 39 | 1303 |
| Incidence rate | 0.15(0.11-0.21) | 0.27(0.25-0.28) |
| Liver & Biliary tract cancer | |  |
| No. of cancers | 25 | 725 |
| Incidence rate | 0.10(0.07-0.14) | 0.15(0.14-0.16) |
| Esophagus cancer |  |  |
| No. of cancers | 30 | 843 |
| Incidence rate | 0.12(0.08-0.17) | 0.17(0.16-0.19) |
| Stomach cancer |  |  |
| No. of cancers | 27 | 576 |
| Incidence rate | 0.11(0.07-0.15) | 0.12(0.11-0.13) |
| Other digestive cancers | |  |
| No. of cancers | 74 | 1675 |
| Incidence rate | 0.29(0.23-0.36) | 0.35(0.33-0.36) |

Note: IBS: irritable bowel syndrome.

**Figure S2. Cumulative incidence of each type of digestive cancer in patients with IBS and reference individuals (estimated by Kaplan-Meier method). A. Colorectal cancer; B. Colon cancer; C. Rectal cancer; D. Liver & biliary tract cancer; E. Esophagus cancer; F. Stomach cancer; G. other digestive cancer.** IBS: irritable bowel syndrome. Due to dramatically decreased sample size of IBS group after 14 years’ follow-up, the 15-year cumulative incidence of other digestive cancer abruptly increased to 1.6%, accompanied with wide confidence interval (95%CI: 0.3%-2.9%).

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**D. Liver & biliary tract cancer**

**C. Rectal cancer**

**B. Colon cancer**

**A. Colorectal cancer**

****

****

**G. Other digestive cancer**

**F. Stomach cancer**

**E. Esophagus cancer**

**Table S7.** **Sensitivity analysis for the association between IBS and incidence of overall cancers with cancer-specific mortality.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **No. of events** | **No. of participants** | **adjusted HR (95%CI)** | **P value** |
| **Outcome: overall cancers** | | | | |
| Sensitivity analysis 1: excluding IBS participants diagnosed after recruitment in non-IBS group (N=441824) | | | | |
| Non-IBS | 59319 | 419486 | Reference |  |
| IBS | 2937 | 22338 | 0.97 (0.93-1.01) | 0.092 |
| Sensitivity analysis 2: excluding incident cancer participants during 1 year after study baseline (N=448775) | | | | |
| Non-IBS | 59747 | 426448 | Reference |  |
| IBS | 2926 | 22327 | 0.98 (0.94-1.01) | 0.232 |
| Sensitivity analysis 3: excluding incident cancer participants during 2 years after study baseline (N=448665) | | | | |
| Non-IBS | 59654 | 426355 | Reference |  |
| IBS | 2909 | 22310 | 0.97 (0.94-1.01) | 0.166 |
| Sensitivity analysis 4: competing risk model (N=449595, No. of competing events=14951) | | | | |
| Non-IBS | 60556 | 427257 | Reference |  |
| IBS | 2937 | 22338 | 0.97 (0.94-1.01) | 0.115 |
| **Outcome: cancer specific mortality** | | | | |
| Sensitivity analysis 1: excluding IBS participants diagnosed after recruitment in non-IBS group (N=441824) | | | | |
| Non-IBS | 12039 | 419486 | Reference |  |
| IBS | 512 | 22338 | 0.83 (0.76-0.91) | <0.001 |
| Sensitivity analysis 2: excluding incident cancer participants during 1 year after study baseline (N=448775) | | | | |
| Non-IBS | 12144 | 426448 | Reference |  |
| IBS | 508 | 22327 | 0.83 (0.76-0.91) | <0.001 |
| Sensitivity analysis 3: excluding incident cancer participants during 2 years after study baseline (N=448665) | | | | |
| Non-IBS | 12124 | 426355 | Reference |  |
| IBS | 506 | 22310 | 0.83 (0.76-0.91) | <0.001 |
| Sensitivity analysis 4: competing risk model (N=449595, No. of competing events=16170) | | | | |
| Non-IBS | 12282 | 427257 | Reference |  |
| IBS | 512 | 22338 | 0.84 (0.77-0.92) | <0.001 |

Note: All adjusted HRs were calculated by adjusting the following covariates: age, gender, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, IPAQ (International Physical Activity Questionnaire), diabetes, long-standing illness, overall health rating and family history of cancer; IBS: irritable bowel syndrome; HR: hazard ratio; CI: confidence interval.

**Table S8.** **SMD before PS matching and after PS matching in the whole population.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Before PS matching** | | | **After PS matching** | | |
|  | **Non-IBS** | **IBS** | **SMD** | **Non-IBS** | **IBS** | **SMD** |
| N | 427257 | 22338 |  | 207830 | 20783 |  |
| Age (mean (SD)) | 56.22 (8.12) | 55.98 (7.92) | 0.030 | 56.08 (8.08) | 56.04 (7.94) | 0.005 |
| Female (%) | 223171 (52.2) | 16345 (73.2) | 0.443 | 147670 (71.1) | 14791 (71.2) | 0.003 |
| Ethnicity |  |  | 0.108 |  |  | 0.004 |
| Non-White | 25622 (6.0) | 824 (3.7) |  | 8345 (4.0) | 818 (3.9) |  |
| White | 399996 (93.6) | 21438 (96.0) |  | 198754 (95.6) | 19892 (95.7) |  |
| Unknown | 1639 (0.4) | 76 (0.3) |  | 731 (0.4) | 73 (0.4) |  |
| Family history of cancers (first-order relatives) | | | 0.040 |  |  | <0.001 |
| Yes | 146592 (34.3) | 8093 (36.2) |  | 74722 (36.0) | 7476 (36.0) |  |
| Education level |  |  | 0.070 |  |  | 0.001 |
| Non-university | 279290 (65.4) | 15282 (68.4) |  | 140960 (67.8) | 14107 (67.9) |  |
| University | 139206 (32.6) | 6714 (30.1) |  | 63560 (30.6) | 6346 (30.5) |  |
| Unknown | 8761 (2.0) | 342 (1.5) |  | 3310 (1.6) | 330 (1.6) |  |
| Townsend deprivation index | | | 0.020 |  |  | 0.005 |
| Q1(≤ -3.63) | 106728 (25.0) | 5703 (25.5) |  | 53355 (25.7) | 5326 (25.6) |  |
| Q2(-3.63 - -2.12) | 106476 (24.9) | 5640 (25.2) |  | 52794 (25.4) | 5273 (25.4) |  |
| Q3(-2.12 - 0.58) | 106709 (25.0) | 5520 (24.7) |  | 51180 (24.6) | 5158 (24.8) |  |
| Q4 (>0.58) | 106803 (25.0) | 5452 (24.4) |  | 50280 (24.2) | 5003 (24.1) |  |
| Unknown | 541 (0.1) | 23 (0.1) |  | 221 (0.1) | 23 (0.1) |  |
| Smoking status |  |  | 0.026 |  |  | 0.002 |
| Never | 234389 (54.9) | 12504 (56.0) |  | 116049 (55.8) | 11589 (55.8) |  |
| Previous | 144911 (33.9) | 7474 (33.5) |  | 69905 (33.6) | 7008 (33.7) |  |
| Current | 45439 (10.6) | 2242 (10.0) |  | 20756 (10.0) | 2076 (10.0) |  |
| Unknown | 2518 (0.5) | 118 (0.5) |  | 1120 (0.5) | 110 (0.5) |  |
| Alcohol drinking |  |  | 0.084 |  |  | 0.004 |
| Never | 18989 (4.4) | 1074 (4.8) |  | 9792 (4.7) | 981 (4.7) |  |
| Previous | 14730 (3.4) | 1134 (5.1) |  | 9193 (4.4) | 937 (4.5) |  |
| Current | 392088 (91.8) | 20065 (89.8) |  | 188234 (90.6) | 18803 (90.5) |  |
| Unknown | 1450 (0.3) | 65 (0.3) |  | 611 (0.3) | 62 (0.3) |  |
| IPAQ (%) |  |  | 0.094 |  |  | 0.003 |
| Low | 64220 (15.0) | 3690 (16.5) |  | 32944 (15.9) | 3310 (15.9) |  |
| Moderate | 139753 (32.7) | 7111 (31.9) |  | 67134 (32.3) | 6715 (32.3) |  |
| High | 139515 (32.7) | 6549 (29.3) |  | 62231 (29.9) | 6228 (30.0) |  |
| Unknown | 83769 (19.6) | 4988 (22.3) |  | 45521 (21.9) | 4530 (21.8) |  |
| BMI |  |  | 0.084 |  |  | 0.008 |
| <18.5 kg/m2 | 2071 (0.5) | 191 (0.9) |  | 1556 (0.7) | 144 (0.7) |  |
| 18.5-24.9 kg/m2 | 132446 (31.0) | 7538 (33.7) |  | 69799 (33.6) | 7020 (33.8) |  |
| 24.9-29.9 kg/m2 | 183254 (42.9) | 8879 (39.7) |  | 83829 (40.3) | 8343 (40.1) |  |
| ≥30 kg/m2 | 106806 (25.0) | 5619 (25.2) |  | 51595 (24.8) | 5171 (24.9) |  |
| Unknown | 2680 (0.6) | 111 (0.5) |  | 1051 (0.5) | 105 (0.5) |  |
| Long-standing illness | |  | 0.314 |  |  | 0.004 |
| No | 290807 (68.1) | 11825 (52.9) |  | 117339 (56.5) | 11777 (56.7) |  |
| Yes | 125527 (29.4) | 9742 (43.6) |  | 83520 (40.2) | 8313 (40.0) |  |
| Unknown | 10923 (2.6) | 771 (3.5) |  | 6971 (3.4) | 693 (3.3) |  |
| Overall health rating | |  | 0.358 |  |  | 0.007 |
| Excellent | 73879 (17.3) | 1962 (8.8) |  | 19919 (9.6) | 1962 (9.4) |  |
| Good | 248425 (58.1) | 11887 (53.2) |  | 117302 (56.4) | 11770 (56.6) |  |
| Fair | 85001 (19.9) | 6476 (29.0) |  | 55838 (26.9) | 5557 (26.7) |  |
| Poor | 17052 (4.0) | 1855 (8.3) |  | 13293 (6.4) | 1348 (6.5) |  |
| Unknown | 2900 (0.7) | 158 (0.7) |  | 1478 (0.7) | 146 (0.7) |  |
| Diabetes (%) | 35036 (8.2) | 1888 (8.5) | 0.009 | 17144 (8.2) | 1722 (8.3) | 0.001 |

Note: Numbers are n (%) unless otherwise stated. IBS: irritable bowel syndrome; IPAQ: International Physical Activity Questionnaire; BMI: body mass index; PS: propensity score; SMD: standardized mean difference.

**Table S9.** **SMD before and after PS inverse probability weighting in the whole population.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Before PS IPTW** | | | **After PS IPTW** | | |
|  | **Non-IBS** | **IBS** | **SMD** | **Non-IBS** | **IBS** | **SMD** |
| N | 427257 | 22338 |  | 449591.4 | 452142.7 |  |
| Age (mean (SD)) | 56.22 (8.12) | 55.98 (7.92) | 0.030 | 56.21 (8.12) | 56.22 (7.94) | 0.001 |
| Female (%) | 223171 (52.2) | 16345 (73.2) | 0.443 | 239509.0 (53.3) | 237785.4 (52.6) | 0.014 |
| Ethnicity |  |  | 0.108 |  |  | 0.022 |
| Non-White | 25622 (6.0) | 824 (3.7) |  | 26447.4 (5.9) | 28169.9 (6.2) |  |
| White | 399996 (93.6) | 21438 (96.0) |  | 421428.2 (93.7) | 421775.4 (93.3) |  |
| Unknown | 1639 (0.4) | 76 (0.3) |  | 1715.8 (0.4) | 2197.5 (0.5) |  |
| Family history of cancers (first-order relatives) | | | 0.040 |  |  | 0.001 |
| Yes | 146592 (34.3) | 8093 (36.2) |  | 154682.0 (34.4) | 155732.0 (34.4) |  |
| Education level |  |  | 0.070 |  |  | 0.035 |
| Non-university | 279290 (65.4) | 15282 (68.4) |  | 294549.9 (65.5) | 288760.1 (63.9) |  |
| University | 139206 (32.6) | 6714 (30.1) |  | 145938.8 (32.5) | 154271.8 (34.1) |  |
| Unknown | 8761 (2.0) | 342 (1.5) |  | 9102.7 (2.0) | 9110.9 (2.0) |  |
| Townsend deprivation index | | | 0.020 |  |  | 0.016 |
| Q1(≤ -3.63) | 106728 (25.0) | 5703 (25.5) |  | 112436.4 (25.0) | 114078.2 (25.2) |  |
| Q2(-3.63 - -2.12) | 106476 (24.9) | 5640 (25.2) |  | 112118.7 (24.9) | 113629.9 (25.1) |  |
| Q3(-2.12 - 0.58) | 106709 (25.0) | 5520 (24.7) |  | 112228.3 (25.0) | 113994.8 (25.2) |  |
| Q4 (>0.58) | 106803 (25.0) | 5452 (24.4) |  | 112243.9 (25.0) | 109864.0 (24.3) |  |
| Unknown | 541 (0.1) | 23 (0.1) |  | 564.1 (0.1) | 575.8 (0.1) |  |
| Smoking status |  |  | 0.026 |  |  | 0.018 |
| Never | 234389 (54.9) | 12504 (56.0) |  | 246888.0 (54.9) | 248123.8 (54.9) |  |
| Previous | 144911 (33.9) | 7474 (33.5) |  | 152391.5 (33.9) | 155170.0 (34.3) |  |
| Current | 45439 (10.6) | 2242 (10.0) |  | 47675.1 (10.6) | 45895.2 (10.2) |  |
| Unknown | 2518 (0.5) | 118 (0.5) |  | 2636.8 (0.6) | 2953.8 (0.7) |  |
| Alcohol drinking |  |  | 0.084 |  |  | 0.014 |
| Never | 18989 (4.4) | 1074 (4.8) |  | 20060.3 (4.5) | 19575.6 (4.3) |  |
| Previous | 14730 (3.4) | 1134 (5.1) |  | 15865.6 (3.5) | 16365.1 (3.6) |  |
| Current | 392088 (91.8) | 20065 (89.8) |  | 412149.8 (91.7) | 414371.2 (91.6) |  |
| Unknown | 1450 (0.3) | 65 (0.3) |  | 1515.8 (0.3) | 1830.8 (0.4) |  |
| IPAQ (%) |  |  | 0.094 |  |  | 0.006 |
| Low | 64220 (15.0) | 3690 (16.5) |  | 67910.4 (15.1) | 68928.8 (15.2) |  |
| Moderate | 139753 (32.7) | 7111 (31.9) |  | 146866.2 (32.7) | 147981.0 (32.7) |  |
| High | 139515 (32.7) | 6549 (29.3) |  | 146064.9 (32.5) | 146788.9 (32.5) |  |
| Unknown | 83769 (19.6) | 4988 (22.3) |  | 88750.0 (19.7) | 88444.1 (19.6) |  |
| BMI |  |  | 0.084 |  |  | 0.015 |
| <18.5 kg/m2 | 2071 (0.5) | 191 (0.9) |  | 2261.1 (0.5) | 2134.0 (0.5) |  |
| 18.5-24.9 kg/m2 | 132446 (31.0) | 7538 (33.7) |  | 139992.2 (31.1) | 143304.7 (31.7) |  |
| 24.9-29.9 kg/m2 | 183254 (42.9) | 8879 (39.7) |  | 192135.2 (42.7) | 192993.5 (42.7) |  |
| ≥30 kg/m2 | 106806 (25.0) | 5619 (25.2) |  | 112412.3 (25.0) | 111112.5 (24.6) |  |
| Unknown | 2680 (0.6) | 111 (0.5) |  | 2790.6 (0.6) | 2598.1 (0.6) |  |
| Long-standing illness | |  | 0.314 |  |  | 0.003 |
| No | 290807 (68.1) | 11825 (52.9) |  | 302630.6 (67.3) | 305051.1 (67.5) |  |
| Yes | 125527 (29.4) | 9742 (43.6) |  | 135267.7 (30.1) | 135432.8 (30.0) |  |
| Unknown | 10923 (2.6) | 771 (3.5) |  | 11693.1 (2.6) | 11658.8 (2.6) |  |
| Overall health rating | |  | 0.358 |  |  | 0.020 |
| Excellent | 73879 (17.3) | 1962 (8.8) |  | 75842.4 (16.9) | 78882.9 (17.4) |  |
| Good | 248425 (58.1) | 11887 (53.2) |  | 260316.0 (57.9) | 261900.8 (57.9) |  |
| Fair | 85001 (19.9) | 6476 (29.0) |  | 91470.0 (20.3) | 89590.4 (19.8) |  |
| Poor | 17052 (4.0) | 1855 (8.3) |  | 18904.6 (4.2) | 18509.2 (4.1) |  |
| Unknown | 2900 (0.7) | 158 (0.7) |  | 3058.4 (0.7) | 3259.4 (0.7) |  |
| Diabetes (%) | 35036 (8.2) | 1888 (8.5) | 0.009 | 36918.8 (8.2) | 36330.8 (8.0) | 0.006 |

Note: Numbers are n (%) unless otherwise stated. IBS: irritable bowel syndrome; IPAQ: International Physical Activity Questionnaire; BMI: body mass index; PS: propensity score; SMD: standardized mean difference; IPTW: inverse probability weighting.

**Table S10.** **Association between IBS and incidence of overall cancers with cancer specific mortality estimated from propensity score method.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **No. of events** | **No. of participants** | **adjusted HR (95%CI)** | **P value** |
| **Outcome: overall cancers** | | | | |
| Propensity score matching (1:10 matching, N=228613) | | | | |
| Non-IBS | 28476 | 207830 | Reference |  |
| IBS | 2771 | 20783 | 0.97 (0.93-1.01) | 0.090 |
| Propensity score adjustment (N=449595) | | | | |
| Non-IBS | 60556 | 427257 | Reference |  |
| IBS | 2937 | 22338 | 0.96 (0.92-1.00) | 0.032 |
| Propensity score inverse probability weighting (before weighting: N=449595; after weighting: N=901734.1) | | | | |
| Non-IBS | 62942.8 | 449591.4 | Reference |  |
| IBS | 63300.0 | 452142.7 | 0.97 (0.93-1.02) | 0.242 |
| **Outcome: cancer specific mortality** | | | | |
| Propensity score matching (1:10 matching, N=228613) | | | | |
| Non-IBS | 5751 | 207830 | Reference |  |
| IBS | 477 | 20783 | 0.82 (0.75-0.90) | <0.001 |
| Propensity score adjustment (N=449595) | | | | |
| Non-IBS | 12282 | 427257 | Reference |  |
| IBS | 512 | 22338 | 0.82 (0.75-0.89) | <0.001 |
| Propensity score inverse probability weighting (before weighting: N=449595; after weighting: N=901734.1) | | | | |
| Non-IBS | 13487.7 | 449591.4 | Reference |  |
| IBS | 9042.9 | 452142.7 | 0.77 (0.69-0.86) | <0.001 |

Note: Propensity score was calculated by including the following covariates in the logistic model: age, gender, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, IPAQ (International Physical Activity Questionnaire), diabetes, long-standing illness, overall health rating and family history of cancer; IBS: irritable bowel syndrome; HR: hazard ratio; CI: confidence interval.

**Table S11.** **Sensitivity analysis for the association between IBS and site-specific cancers by competing risk model (N=449595).**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type of cancer** | **No. of cancers** | **No. of competing events** | **No. of participants** | **adjusted HR**  **(95%CI)** | **P value** |
| Digestive (No. of competing events=70037) | | | | | |
| Non-IBS | 8104 | 66783 | 427257 | Reference |  |
| IBS | 306 | 3254 | 22338 | 0.80 (0.71-0.90) | <0.001 |
| Central nerval system (No. of competing events=77627) | | | | | |
| Non-IBS | 776 | 74108 | 427257 | Reference |  |
| IBS | 41 | 3519 | 22338 | 1.15 (0.84-1.58) | 0.378 |
| Thyroid & endocrine (No. of competing events=78053) | | | | | |
| Non-IBS | 371 | 74513 | 427257 | Reference |  |
| IBS | 20 | 3540 | 22338 | 0.85 (0.54-1.34) | 0.491 |
| Skin (No. of competing events=57396) | | | | | |
| Non-IBS | 20076 | 54808 | 427257 | Reference |  |
| IBS | 972 | 2588 | 22338 | 1.01 (0.95-1.08) | 0.805 |
| Melanoma (No. of competing events=76024) | | | | | |
| Non-IBS | 2324 | 72560 | 427257 | Reference |  |
| IBS | 96 | 3464 | 22338 | 0.84 (0.69-1.03) | 0.098 |
| Non-melanoma (No. of competing events=59366) | | | | | |
| Non-IBS | 18193 | 56691 | 427257 | Reference |  |
| IBS | 885 | 2675 | 22338 | 1.02 (0.95-1.09) | 0.589 |
| Urinary tract (No. of competing events=76118) | | | | | |
| Non-IBS | 2228 | 72656 | 427257 | Reference |  |
| IBS | 98 | 3462 | 22338 | 1.04 (0.85-1.27) | 0.717 |
| Haematological (No. of competing events=74615) | | | | | |
| Non-IBS | 3662 | 71222 | 427257 | Reference |  |
| IBS | 167 | 3393 | 22338 | 0.94 (0.81-1.10) | 0.459 |
| Breast\* (No. of competing events=27915) | | | | | |
| Non-IBS | 7223 | 26050 | 223171 | Reference |  |
| IBS | 532 | 1865 | 16345 | 1.01 (0.92-1.10) | 0.885 |
| Genital, female\* (No. of competing events=33202) | | | | | |
| Non-IBS | 2334 | 30939 | 223171 | Reference |  |
| IBS | 134 | 2263 | 16345 | 0.79 (0.66-0.94) | 0.009 |
| Genital, male# (No. of competing events=33220) | | | | | |
| Non-IBS | 9290 | 32321 | 204086 | Reference |  |
| IBS | 264 | 899 | 5993 | 1.02 (0.90-1.15) | 0.803 |

Note: \*: adjusted HR was calculated in female participants; #: adjusted HR was calculated in male participants; All adjusted HRs were calculated by adjusting the following covariates: age, gender, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, IPAQ (International Physical Activity Questionnaire), diabetes, long-standing illness, overall health rating and family history of cancer; IBS: irritable bowel syndrome; HR: hazard ratio; CI: confidence interval.