**Supplementary Material**

**Supplementary Table S1.** Characteristics of 219,249 study individuals in the United Kingdom with a first-time plasma B12 measurement and one or more missing values on smoking, alcohol use, BMI or Townsend quintile, 1 January 2000 to 30 June 2015.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Plasma B12 level groups (pmol/L)** | | | |
|  | **150-600** | **601-800** | **801-1000** | **>1000** |
| **No.** | 211,155 | 5,537 | 1,444 | 1,113 |
| **Sex (female), %** | 140,558 (67) | 3,826 (69) | 999 (69) | 780 (70) |
| **Age in years, median (range)** | 51.4 (18-99) | 54.3 (18-99) | 58.6 (18-99) | 62.8 (18-99) |
|  |  |  |  |  |
| **Year of B12 measurement, n (%)a** |  |  |  |  |
| 2000-2004 | 18,991 (9) | 606 (11) | 201 (14) | 165 (15) |
| 2005-2008 | 39,669 (19) | 1,065 (19) | 277 (19) | 244 (22) |
| 2009-2011 | 61,839 (29) | 1,598 (29) | 365 (25) | 279 (25) |
| 2012-mid2015 | 90,656 (43) | 2,268 (41) | 601 (42) | 425 (38) |
|  |  |  |  |  |
| **Smoking, n (%)a** |  |  |  |  |
| Never smoker | 106,701 (51) | 2,979 (54) | 756 (52) | 537 (48) |
| Former smoker | 41,178 (20) | 956 (17) | 215 (15) | 200 (18) |
| Smoker | 38,163 (18) | 788 (14) | 203 (14) | 174 (16) |
| Missing | 25,113 (12) | 814 (15) | 270 (19) | 202 (18) |
|  |  |  |  |  |
| **Alcohol use, n (%)a** |  |  |  |  |
| Non-drinker | 13,298 (6) | 521 (9) | 131 (9) | 87 (8) |
| Former drinker | 1,967 (1) | 66 (1) | 16 (1) | 20 (2) |
| Moderate drinker (within guidelines) | 24,674 (12) | 589 (11) | 151 (10) | 91 (8) |
| Heavy drinker | 3,215 (2) | 66 (1) | 19 (1) | 17 (2) |
| Very heavy drinker | 3,229 (2) | 161 (3) | 56 (4) | 65 (6) |
| Missing | 164,772 (78) | 4,134 (75) | 1,071 (74) | 833 (75) |
|  |  |  |  |  |
| **BMI in categories, n (%)a** |  |  |  |  |
| <18.5 kg/m2 | 6,899 (3) | 287 (5) | 87 (6) | 60 (5) |
| 18.5-24.9 kg/m2 | 65,446 (31) | 1,914 (35) | 464 (32) | 346 (31) |
| 25-29.9 kg/m2 | 47,056 (22) | 1,099 (20) | 308 (21) | 215 (19) |
| ≥30 kg/m2 | 34,657 (16) | 704 (13) | 160 (11) | 121 (11) |
| Missing | 57,097 (27) | 1,533 (28) | 425 (29) | 371 (33) |
|  |  |  |  |  |
| **Townsend quintile, n (%)a** |  |  |  |  |
| 1 | 4562,6 (22) | 1,062 (19) | 257 (18) | 221 (20) |
| 2 | 39,885 (19) | 951 (17) | 249 (17) | 203 (18) |
| 3 | 40,431 (19) | 1,017 (18) | 261 (18) | 232 (21) |
| 4 | 34,021 (16) | 910 (16) | 240 (17) | 184 (17) |
| 5 | 21,977 (10) | 606 (11) | 201 (14) | 125 (11) |
| Missing | 29,215 (14) | 991 (18) | 236 (16) | 148 (13) |

**Supplementary Table S1.** aNumbers do not add up to 100 due to rounding. Abbreviations: BMI: body mass index.

**Supplementary Table S2.** Cumulative incidence proportions, person-years, number of cancer events and incidence rates (all with corresponding 95% confidence intervals) for the risk of cancer in the main study population, restricted to persons with complete data on covariates (n =573,173).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Plasma B12 level groups (pmol/L)** | | | |
| **Main study population** | **150-600** | **601-800** | **801-1000** | **>1000** |
| **CIP in % (95% CI)** |  |  |  |  |
| End of follow-up | 13.87 (13.39-14.35) | 15.52 (12.72-18.58) | 19.69 (11.40-29.65) | 18.63 (13.94-23.85) |
| 1 year of follow-up | 1.61 (1.58-1.65) | 2.34 (2.08-2.62) | 3.66 (3.01-4.39) | 6.28 (5.32-7.34) |
| 2 years of follow-up | 2.54 (2.49-2.58) | 3.43 (3.11-3.78) | 4.68 (3.93-5.52) | 7.52 (6.45-8.69) |
| 5 years of follow-up | 5.25 (5.18-5.33) | 5.71 (5.23-6.22) | 7.65 (6.55-8.86) | 10.31 (8.91-11.82) |
| **Person-years** |  |  |  |  |
| Overall | 2,076,850 | 47,204 | 11,155 | 7,598 |
| <1 year | 484,023 | 11,234 | 2,608 | 1,891 |
| ≥1-≤2 years | 391,714 | 8,933 | 2,069 | 1,426 |
| >2-≤4 years | 730,163 | 16,323 | 3,767 | 2,520 |
| ≥5 years | 470,949 | 10,715 | 2,710 | 1,762 |
| **Cancer events** |  |  |  |  |
| Overall | 24,298 | 646 | 212 | 216 |
| <1 year | 8,066 | 281 | 105 | 140 |
| ≥1-≤2 years | 3,806 | 107 | 24 | 22 |
| >2-≤4 years | 7,284 | 145 | 46 | 32 |
| ≥5 years | 5,142 | 113 | 37 | 22 |
| **IR/1,000 PYs (95% CI)** |  |  |  |  |
| Overall | 11.70 (11.55-11.85) | 13.69 (12.67-14.78) | 19.01 (16.61-21.74) | 28.43 (24.88-32.49) |
| <1 year | 16.66 (16.30-17.03) | 25.01 (22.25-28.12) | 40.26 (33.25-48.75) | 74.05 (62.75-87.39) |
| ≥1-≤2 years | 9.72 (9.41-10.03) | 11.98 (9.91-14.48) | 11.60 (7.77-17.30) | 15.43 (10.16-23.44) |
| >2-≤4 years | 9.98 (9.75-10.21) | 8.88 (7.55-10.45) | 12.21 (9.15-16.30) | 12.70 (8.98-17.96) |
| ≥5 years | 10.92 (10.62-11.22) | 10.55 (8.77-12.68) | 13.65 (9.89-18.84) | 12.49 (8.22-18.97) |

**Supplementary Table S2.** Abbreviations: BMI: body mass index; CI: confidence interval; CIP: cumulative incidence proportion; IR: incidence rate; PYs: person-years.

**Supplementary Table S3.** Cumulative incidence proportions and adjusted incidence rate ratios (all with corresponding 95% confidence intervals) for the 1-year risk of cancer in the main study population, stratified according to several covariates.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Plasma B12 level groups (pmol/L)** | | | | |
| Main study population | **150-600** | **601-800** | | **801-1000** | **>1000** |
| **CIP (95% CI), 1 year of follow-up** |  |  | |  |  |
| Male | 2.36 (2.30-2.42) | 3.06 (2.63-3.54) | | 4.90 (3.82-6.16) | 9.44 (7.77-11.30) |
| Female | 1.18 (1.15-1.21) | 1.95 (1.71-2.21) | | 2.79 (2.24-3.43) | 5.27 (4.39-6.25) |
| Age 18-39 | 0.16 (0.14-0.18) | | 0.28 (0.14-0.50) | 0.36 (0.10-1.01) | 0.36 (0.08-1.24) |
| Age 40-59 | 0.82 (0.78-0.86) | 1.27 (1.01-1.58) | | 1.71 (1.12-2.49) | 4.90 (3.70-6.33) |
| Age 60-79 | 2.80 (2.73-2.87) | 3.96 (3.46-4.51) | | 5.27 (4.17-6.54) | 9.70 (8.04-11.54) |
| Age 80-99 | 3.25 (3.13-3.37) | 4.39 (3.61-5.27) | | 7.81 (5.84-10.14) | 9.43 (7.26-11.94) |
| Non-smoker | 1.32 (1.28-1.35) | 1.85 (1.60-2.13) | | 2.89 (2.28-3.61) | 5.54 (4.55-6.67) |
| Current smoker | 1.50 (1.44-1.57) | 2.38 (1.87-3.00) | | 2.39 (1.45-3.71) | 6.79 (4.90-9.08) |
| Non-drinker | 1.45 (1.38-1.51) | 1.31 (1.00-1.69) | | 2.45 (1.64-3.52) | 4.56 (3.22-6.22) |
| Moderate drinker (within guidelines) | 1.62 (1.58-1.66) | 2.66 (2.31-3.06) | | 4.19 (3.28-5.26) | 7.48 (6.07-9.07) |
| Very heavy drinker | 1.40 (1.25-1.56) | 2.54 (1.62-3.79) | | 1.74 (0.66-3.80) | 4.05 (2.15-6.89) |
| Townsend quintile 1 | 1.69 (1.63-1.75) | 2.91 (2.40-3.50) | | 4.26 (3.06-5.75) | 7.70 (5.85-9.88) |
| Townsend quintile 2 | 1.75 (1.68-1.81) | 2.54 (2.05-3.10) | | 4.64 (3.32-6.29) | 6.01 (4.44-7.90) |
| Townsend quintile 3 | 1.60 (1.53-1.66) | 2.18 (1.73-2.70) | | 4.06 (2.90-5.51) | 6.73 (5.03-8.75) |
| Townsend quintile 4 | 1.57 (1.50-1.64) | 2.12 (1.66-2.66) | | 2.97 (1.95-4.31) | 7.87 (5.94-10.13) |
| Townsend quintile 5 | 1.45 (1.37-1.53) | 1.85 (1.38-2.44) | | 1.64 (0.87-2.84) | 4.05 (2.55-6.06) |
| BMI: 18.5-24.9 kg/m2 | 1.62 (1.57-1.67) | 2.13 (1.81-2.49) | | 3.44 (2.64-4.39) | 6.71 (5.42-8.18) |
| BMI: ≥30 kg/m2 | 1.38 (1.32-1.44) | 2.18 (1.70-2.75) | | 3.63 (2.44-5.19) | 6.33 (4.53-8.54) |
| **Adj. IRRa (95% CI), 1 year of follow-up** |  |  | |  |  |
| Male | Ref. | 1.82 (1.53-2.16) | | 3.16 (2.37-4.20) | 5.00 (3.93-6.36) |
| Female | Ref. | 1.68 (1.43-1.98) | | 2.73 (2.10-3.55) | 4.48 (3.55-5.66) |
| Age 18-39 | Ref. | 2.59 (1.32-5.08) | | 2.35 (0.58-9.52) | . (.-.)\* |
| Age 40-59 | Ref. | 1.52 (1.15-2.02) | | 2.50 (1.59-3.94) | 6.18 (4.32-8.84) |
| Age 60-79 | Ref. | 1.71 (1.46-2.01) | | 2.31 (1.75-3.05) | 4.53 (3.60-5.71) |
| Age 80-99 | Ref. | 1.80 (1.41-2.30) | | 4.57 (3.24-6.46) | 4.60 (3.29-6.43) |
| Non-smoker | Ref. | 1.79 (1.51-2.12) | | 3.05 (2.34-3.97) | 5.24 (4.16-6.58) |
| Current smoker | Ref. | 1.67 (1.25-2.24) | | 2.28 (1.35-3.86) | 3.67 (2.35-5.71) |
| Non-drinker | Ref. | 1.21 (0.92-1.59) | | 2.27 (1.50-3.43) | 3.80 (2.69-5.37) |
| Moderate drinker (within guidelines) | Ref. | 1.98 (1.70-2.30) | | 3.31 (2.59-4.23) | 5.31 (4.26-6.62) |
| Very heavy drinker | Ref. | 1.78 (1.06-3.00) | | 1.47 (0.55-3.95) | 3.89 (2.07-7.33) |
| Townsend quintile 1 | Ref. | 2.11 (1.68-2.65) | | 2.93 (2.00-4.29) | 5.36 (3.83-7.50) |
| Townsend quintile 2 | Ref. | 1.78 (1.39-2.28) | | 2.99 (1.98-4.51) | 4.59 (3.18-6.63) |
| Townsend quintile 3 | Ref. | 1.37 (1.03-1.84) | | 3.30 (2.24-4.87) | 5.31 (3.76-7.50) |
| Townsend quintile 4 | Ref. | 1.62 (1.22-2.14) | | 3.03 (1.92-4.76) | 4.82 (3.36-6.93) |
| Townsend quintile 5 | Ref. | 1.85 (1.35-2.53) | | 1.92 (1.03-3.59) | 2.99 (1.73-5.17) |
| BMI: 18.5-24.9 kg/m2 | Ref. | 1.59 (1.32-1.92) | | 3.01 (2.26-4.00) | 5.10 (3.97-6.55) |
| BMI: ≥30 kg/m2 | Ref. | | 1.84 (1.39-2.43) | 3.63 (2.38-5.53) | 5.78 (4.00-8.35) |

**Supplementary Table S3.** aIncidence rate ratios were based on the 537,936 persons with complete data on all covariates. Estimates were computed using persons with a plasma B12 level of 150-600 pmol/L as reference and adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. The analyses were stratified according to plasma B12 levels and length of follow-up. \*Too few events to compute estimates. Abbreviations: BMI: body mass index; CI: confidence interval; CIP: cumulative incidence proportion; IRR: incidence rate ratio.

**Supplementary Table S4.** Adjusted incidence rate ratios (all with corresponding 95% confidence intervals) for the risk of specific cancer types in the main study population.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Plasma B12 level groups (pmol/L)** | | | |
| **Cancer type** | **150-600** | **601-800** | **801-1000** | **>1000** |
| **Breast, n** | 4,607 | 123 | 36 | 27 |
| Overall | Ref. | 1.11 (0.90-1.38) | 1.62 (1.13-2.32) | 1.51 (.97-2.34) |
| <1 year | Ref. | 1.14 (0.73-1.78) | 2.68 (1.48-4.86) | 2.65 (1.32-5.33) |
| **Bladder, n** | 1,293 | 31 | ≤5 | 7 |
| Overall | Ref. | 1.33 (0.89-2.00) | 1.28 (0.53-3.09) | 1.78 (0.80-3.97) |
| <1 year | Ref. | 1.29 (0.57-2.89) | . (.-.)\* | . (.-.)\* |
| **Malignant melanoma, n** | 952 | 23 | 6 | 6 |
| Overall | Ref. | 0.98 (0.59-1.63) | 1.70 (0.76-3.79) | 1.55 (0.58-4.14) |
| <1 year | Ref. | 1.77 (0.72-4.31) | . (.-.)\* | . (.-.)\* |
| **Lymphoma, n** | 1,227 | 29 | 7 | 6 |
| Overall | Ref. | 1.26 (0.84-1.89) | 0.92 (0.34-2.45) | 1.86 (0.83-4.15) |
| <1 year | Ref. | 1.53 (0.84-2.79) | . (.-.)\* | . (.-.)\* |

**Supplementary Table S4.** Incidence rate ratios were based on the 537,936 persons with complete data on all covariates. Estimates were computed using persons with plasma levels B12 of 150-600 pmol/L as reference and adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. The analyses were stratified according to plasma B12 levels and length of follow-up (overall and <1 year). Abbreviations: BMI: body mass index. \*Too few events to compute estimates.

**Supplementary Table S5.** Characteristics of 10,775 first-time statin users with a plasma B12 measurement, 1 January 2000 to 30 June 2015.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Plasma B12 level groups (pmol/L)** | | | |
| First-time statin users | **150-600** | **601-800** | **801-1000** | **>1000** |
| **No** | 10,422 | 241 | 61 | 51 |
| **Sex (female), %** | 5,332 (51) | 142 (59) | 33 (54) | 36 (71) |
| **Age in years, median(range)** | 66.3 (18-99) | 67.8 (23-94) | 66.7 (30-97) | 66.0 (30-91) |
|  |  |  |  |  |
| **Year of B12 measurement, n (%)** |  |  |  |  |
| 2000-2004 | 911 (9) | 16 (7) | 9 (15) | 10 (20) |
| 2005-2008 | 2,990 (29) | 74 (31) | 15 (25) | 12 (24) |
| 2009-2011 | 3,407 (33) | 77 (32) | 18 (30) | 17 (33) |
| 2012-mid2015 | 3,114 (30) | 74 (31) | 19 (31) | 12 (24) |
|  |  |  |  |  |
| **Smoking, n (%)a** |  |  |  |  |
| Never smoker | 4,736 (45) | 124 (51) | 29 (48) | 26 (51) |
| Former smoker | 3,452 (33) | 85 (35) | 20 (33) | 18 (35) |
| Smoker | 2,074 (20) | 30 (12) | 12 (20) | 5 (10) |
| Missing | 160 (2) | 2 (1) | - | 2 (4) |
|  |  |  |  |  |
| **Alcohol use, n (%)a** |  |  |  |  |
| Non-drinker | 2,125 (20) | 73 (30) | 10 (16) | 9 (18) |
| Former drinker | 458 (4) | 9 (4) | 1 (2) | 1 (2) |
| Moderate drinker (Within guidelines) | 5,076 (49) | 105 (44) | 30 (49) | 23 (45) |
| Heavy drinker | 696 (7) | 10 (4) | 3 (5) | 3 (6) |
| Very heavy drinker | 340 (3) | 5 (2) | 3 (5) | - |
| Missing | 1,727 (17) | 39 (16) | 14 (23) | 15 (29) |
|  |  |  |  |  |
| **BMI in categories, n (%)a** |  |  |  |  |
| <18.5 kg/m2 | 201 (2) | 9 (3) | 4 (7) | 1 (2) |
| 18.5-24.9 kg/m2 | 3,021 (29) | 85 (35) | 21 (34) | 18 (35) |
| 25-29.9 kg/m2 | 3,637 (35) | 73 (30) | 24 (39) | 15 (29) |
| ≥30 kg/m2 | 3,053 (29) | 57 (24) | 11 (18) | 13 (25) |
| Missing | 510 (5) | 17 (7) | 1 (2) | 4 (8) |
|  |  |  |  |  |
| **Townsend quintile, n (%)a** |  |  |  |  |
| 1 | 2,359 (23) | 45 (19) | 12 (20) | 12 (24) |
| 2 | 2,159 (21) | 54 (22) | 12 (20) | 10 (20) |
| 3 | 2,109 (20) | 50 (21) | 13 (21) | 11 (22) |
| 4 | 2,016 (19) | 44 (18) | 11 (18) | 10 (20) |
| 5 | 1,394 (13) | 36 (15) | 11 (18) | 53 (10) |
| Missing | 385 (4) | 12 (5) | 2 (3) | 3 (6) |

**Supplementary Table S5.** aNumbers do not add up to 100 due to rounding. Abbreviations: BMI: body mass index.