**Supplemental Table S1**: ORs (95% CI) for risk of CRC by quartiles of baseline biomarkers of anti-LPS- and anti-flagellin-IgA and IgG

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Serum Immunoglobulins Against LPS and Flagellin, OD | Continuous | Quartiles\* | | | | Ptrend |
| (per 1-SD Increase)  OR(95% CI) | Q1  OR | Q2  OR (95% CI) | Q3  OR (95% CI) | Q4  OR (95% CI) |
| Anti-Flic-IgA, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | 1,065/1,065  0.72  0.95 (0.87-1.05)  0.93 (0.84-1.03) | 270/267  < 0.81  1.00  1.00 | 279/267  > 0.81 to < 1.18  1.02 (0.81-1.30)  1.02 (0.80-1.31) | 269/265  > 1.18 to < 1.68  0.99 (0.77-1.27)  0.99 (0.77-1.29) | 247/266  > 1.68  0.91 (0.70-1.17)  0.88 (0.67-1.15) | 0.43  0.34 |
| Anti-Flic-IgG, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | 1,065/1,065  0.78  0.96 (0.88-1.06)  0.99 (0.89-1.09) | 276/267  < 1.46  1.00  1.00 | 260/266  >1.46 to < 1.98  0.94 (0.74-1.20)  0.97 (0.75-1.25) | 262/266  > 1.98 to < 2.58  0.95 (0.73-1.22)  1.00 (0.76-1.30) | 267/266  > 2.58  0.97 (0.75-1.25)  1.03 (0.78-1.34) | 0.82  0.80 |
| Anti-LPS-IgA, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | 1,065/1,065  0.72  1.01 (0.92-1.11)  0.99 (0.89-1.09) | 283/267  < 1.21  1.00  1.00 | 277/267  > 1.21 to < 1.66  0.96 (0.74-1.24)  0.92 (0.71-1.20) | 222/265  > 1.66 to < 2.13  0.78 (0.60-1.01)  0.73 (0.56-0.96) | 283/266  > 2.13  0.98 (0.75-1.28)  0.91 (0.69-1.20) | 0.59  0.29 |
| Anti-LPS-IgG, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb  Total-Anti-Flic, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb  Total-Anti-LPS, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb  Total-Anti-Flic & LPS, no. Ca/Co  SD/Cut-point  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | 1,065/1,065  0.61  1.02 (0.93-1.11)  1.03 (0.94-1.13)  1,065/1,065  1.23  0.95 (0.86-1.04)  0.95 (0.86-1.05)  1,065/1,065  1.11  1.02 (0.93-1.12)  1.01 (0.91-1.12)  1,065/1,065  2.00  0.98 (0.89-1.07)  0.97 (0.88-1.08) | 287/268  < 1.06  1.00  1.00  276/267  < 2.47  1.00  1.00  282/267  < 2.41  1.00  1.00  260/267  < 5.13  1.00  1.00 | 231/265  > 1.06 to < 1.36  0.80 (0.63-1.03)  0.86 (0.67-1.12)  249/266  > 2.47 to < 3.19  0.91 (0.71-1.15)  0.92 (0.72-1.18)  232/266  > 2.41 to < 3.04  0.83 (0.65-1.06)  0.85 (0.65-1.10)  267/265  > 5.13 to < 6.35  1.03 (0.82-1.31)  1.05 (0.82-1.34) | 281/266  > 1.36 to < 1.84  0.98 (0.77-1.26)  1.01 (0.78-1.31)  270/265  >3.19 to < 4.05  0.98 (0.77-1.25)  1.05 (0.82-1.35)  266/265  > 3.04 to < 3.87  0.95 (0.74-1.22)  0.93 (0.72-1.21)  267/267  > 6.35 to < 7.73  1.03 (0.81-1.31)  1.04 (0.81-1.33) | 266/266  > 1.84  0.93 (0.72-1.20)  0.97 (0.74-1.27)  270/267  > 4.05  0.98 (0.76-1.26)  0.99 (0.76-1.30)  285/267  > 3.87  1.02 (0.79-1.33)  1.00 (0.76-1.32)  271/266  > 7.73  1.05 (0.81-1.37)  1.06 (0.81-1.40) | 0.93  0.89  0.97  0.79  0.64  0.84  0.72  0.68 |

Abbreviation: OD = optical density; SD = standard deviation; OR = odds ratio; CI = confidence interval; Flic = flagellin;

Ca/Co = case/control; Total-Anti-Flic = anti-flagellin-IgA + anti-flagellin-IgG; Total-Anti-LPS = anti-LPS-IgA + anti-LPS-IgG; Total-Anti-Flic & LPS = anti-flagellin-IgA + anti-flagellin-IgG + anti-LPS-IgA + anti-LPS-IgG

\*Quartile cut-off points were based on the distribution of controls, expressed as optical density readings

ƗPtrend test was based on median values of each quartile

ᵃMatching-adjusted model based on logistic regression conditioned on matching factors (age, gender, administrative centre and date of blood collection)

ᵇBased on matching factors plus adjustments for established confounding factors (smoking, alcohol consumption, body mass index, waist circumference, physical activity, education, and total daily dietary energy consumption, fibre intake, fruits and vegetable intakes, meat and processed meat consumption)

**Supplemental Table S2:** ORs (95% CI) for risk of CRC by increasing levels of total bacterial exposure and high sensitivity C-reactive protein, waist circumference, BMI, total dietary fat, and alcohol intake; stratified by sex\*

|  |  |  |  |
| --- | --- | --- | --- |
| MEN | | | |
| Total-Anti-Flic & LPS, OD | hs-CRP Low | hs-CRP High | pinteraction |
|  | <2.23 mg/L | >2.23 mg/L |  |
| Tertile 1 (<5.58) | 1.00 | 1.59 (0.98-2.57) | 0.002 |
| Tertile 2 (5.58 to <7.19) | 0.96 (0.61-1.51) | 1.51 (0.95-2.40) |  |
| Tertile 3 (>7.19) | 1.58 (0.97-2.56) | 2.35 (1.45-3.81) |  |
| Total-Anti-Flic & LPS, OD | WC Low | WC High | pinteraction |
| < 96 cm | > 96 cm |  |
| Tertile 1 (<5.58) | 1.00 | 1.66 (1.05-2.63) | 0.010 |
| Tertile 2 (5.58 to <7.19) | 1.04 (0.68-1.61) | 1.53 (0.99-2.38) |  |
| Tertile 3 (>7.19) | 1.56 (0.97-2.50) | 1.97 (1.24-3.13) |  |
| Total-Anti-Flic & LPS, OD | BMI Low | BMI High | pinteraction |
|  | < 26.8 kg/m2 | > 26.8 kg/m2 |  |
| Tertile 1 (<5.58) | 1.00 | 1.55 (0.99-2.42) | 0.032 |
| Tertile 2 (5.58 to <7.19) | 1.19 (0.78-1.82) | 1.24 (0.80-1.90) |  |
| Tertile 3 (>7.19) | 1.60 (1.00-2.55) | 1.77 (1.13-2.78) |  |
| Total-Anti-Flic & LPS, OD | Total Dietary Fat Low | Total Dietary Fat High | pinteraction |
|  | < 86.1 g/day | > 86.1 g/day |  |
| Tertile 1 (<5.58) | 1.00 | 1.35 (0.86-2.14) | 0.097 |
| Tertile 2 (5.58 to <7.19) | 1.27 (0.82-1.96) | 1.02 (0.65-1.58) |  |
| Tertile 3 (>7.19) | 1.70 (1.08-2.65) | 1.50 (0.94-2.37) |  |
| Total-Anti-Flic & LPS, OD | Alcohol Low | Alcohol High | pinteraction |
| < 16. 8 g/day | > 16.8 g/day |
| Tertile 1 (<5.58) | 1.00 | 1.24 (0.80-1.91) | 0.020 |
| Tertile 2 (5.58 to <7.19) | 0.97 (0.83-1.49) | 1.23 (0.79-1.92) |  |
| Tertile 3 (>7.19) | 1.36 (0.87-2.12) | 1.71 (1.09-2.69) |  |
| WOMEN | | | |
| Total-Anti-Flic & LPS, OD | hs-CRP Low | hs-CRP High | pinteraction |
|  | < 2.78 mg/L | > 2.78 mg/L |  |
| Tertile 1 (<5.58) | 1.00 | 1.14 (0.72-1.79) | 0.697 |
| Tertile 2 (5.58 to <7.19) | 0.67 (0.42-1.07) | 1.08 (0.68-1.73) |  |
| Tertile 3 (>7.19) | 0.79 (0.49-1.26) | 1.02 (0.64-1.61) |  |
| Total-Anti-Flic & LPS, OD | WC Low | WC High | pinteraction |
|  | < 81 cm | > 81 cm |  |
| Tertile 1 (<5.58) | 1.00 | 1.66 (1.07-2.57) | 0.753 |
| Tertile 2 (5.58 to <7.19) | 0.90 (0.59-1.38) | 1.26 (0.82-1.93) |  |
| Tertile 3 (>7.19) | 1.04 (0.66-1.61) | 1.14 (0.74-1.75) |  |
| Total-Anti-Flic & LPS, OD | BMI Low | BMI High | pinteraction |
|  | <25.4 kg/m2 | > 25.4 kg/m2 |  |
| Tertile 1 (<5.58) | 1.00 | 1.42 (0.93-2.17) | 0.364 |
| Tertile 2 (5.58 to <7.19) | 0.97 (0.65-1.45) | 0.98 (0.64-1.51) |  |
| Tertile 3 (>7.19) | 1.02 (0.65-1.58) | 0.95 (0.62-1.44) |  |
| Total-Anti-Flic & LPS, OD | Total Dietary Fat Low | Total Dietary Fat High | pinteraction |
|  | < 71.5 g/day | > 71.5 g/day |  |
| Tertile 1 (<5.58) | 1.00 | 0.85 (0.56-1.30) | 0.374 |
| Tertile 2 (5.58 to <7.19) | 0.73 (0.48-1.11) | 0.76 (0.50-1.16) |  |
| Tertile 3 (>7.19) | 0.68 (0.44-1.04) | 0.90 (0.59-1.37) |  |
| Total-Anti-Flic & LPS, OD | Alcohol Low | Alcohol High | pinteraction |
| < 4.2 g/day | > 4.2 g/day |
| Tertile 1 (<5.58) | 1.00 | 0.93 (0.61-1.40) | 0.200 |
| Tertile 2 (5.58 to <7.19) | 0.90 (0.59-1.37) | 0.69 (0.46-1.03) |  |
| Tertile 3 (>7.19) | 0.80 (0.52-1.22) | 0.85 (0.55-1.31) |  |

Abbreviations: LPS = lipopolysaccharide; Flic = flagellin; OD = optical density; hs-CRP = high-sensitivity C-reactive protein; WC = waist circumference; BMI = body mass index; Total-Anti-Flic & LPS = anti-flagellin Ig-A + anti-flagellin IgG + anti-LPS IgA + anti-LPS-IgG

\*Categorized values (high/low and tertile) are based on the values among controls

**Supplemenetal Table S3**: ORs (95% CI) for risk of CRC by quartile of baseline biomarkers of anti-LPS- and anti-flagellin-IgA and IgG after excluding cases and controls that occurred in the first 2 years of follow-up, stratified by sex

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Serum Immunoglobulins against LPS and Flagellin, OD | | Continuous | Quartiles\* | | | | | | Ptrend |
| (per 1-SD Increase)  OR(95% CI) | | Q1  OR | Q2  OR (95% CI) | Q3  OR (95% CI) | Q4  OR (95% CI) | |
| MEN |  | | | | | | | | |
| Anti-Flic-IgA, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 385/385  1.09 (0.94-1.27)  1.05 (0.89-1.24) | | 71/78  1.00  1.00 | 90/104  0.96 (0.63-1.46)  1.09 (0.69-1.72) | 112/99  1.31 (0.84-2.04)  1.51 (0.94-2.43) | 112/104  1.23 (0.79-1.90)  1.26 (0.79-2.02) | | 0.20  0.22 |
| Anti-Flic-IgG, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 385/385  1.00 (0.86-1.16)  1.00 (0.85-1.18) | | 111/107  1.00  1.00 | 90/96  0.90 (0.60-1.34)  0.97 (0.63-1.48) | 93/93  0.96 (0.62-1.46)  1.00 (0.64-1.58) | 91/89  0.99 (0.65-1.51)  1.01 (0.64-1.59) | | 1.00  0.93 |
| Anti-LPS-IgA, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 385/385  1.26 (1.07-1.49)  1.23 (1.03-1.36) | | 89/95  1.00  1.00 | 90/94  1.05 (0.67-1.65)  1.06 (0.66-1.70) | 89/111  0.92 (0.59-1.45)  0.90 (0.56-1.46) | 117/85  1.63 (1.01-2.65)  1.54 (0.91-2.60) | | 0.07  0.17 |
| Anti-LPS-IgG, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-Flic, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-LPS, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-Flic & LPS, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 385/385  1.05 (0.91-1.22)  1.07 (0.91-1.24)  385/385  1.05 (0.90-1.22)  1.03 (0.88-1.21)  385/385  1.19 (1.01-1.40)  1.18 (0.99-1.41)  385/385  1.13 (0.97-1.32)  1.11 (0.94-1.32) | | 106/100  1.00  1.00  97/99  1.00  1.00  93/90  1.00  1.00  83/96  1.00  1.00 | 86/100  0.80 (0.52-1.22)  0.81 (0.52-1.27)  82/93  0.91 (0.61-1.37)  0.97 (0.63-1.48)  82/110  0.74 (0.49-1.12)  0.74 (0.48-1.15)  97/101  1.14 (0.76-1.70)  1.26 (0.82-1.94) | 99/93  0.99 (0.66-1.48)  0.99 (0.64-1.53)  98/100  1.02 (0.68-1.52)  1.14 (0.74-1.74)  90/96  0.97 (0.63-1.50)  0.96 (0.61-1.52)  93/100  1.12 (0.75-1.68)  1.15 (0.75-1.77) | 94/92  0.95 (0.61-1.48)  0.98 (0.62-1.56)  108/93  1.23 (0.80-1.87)  1.24 (0.79-1.94)  120/89  1.48 (0.94-2.33)  1.46 (0.89-2.38)  112/88  1.57 (1.01-2.43)  1.62 (1.01-2.61) | | 0.89  0.81  0.31  0.28  0.05  0.09  0.06  0.09 |
| WOMEN | |  | |  |  | | |  | |  |
| Anti-Flic-IgA, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 431/431  0.90 (0.77-1.05)  0.87 (0.74-1.03) | | 139/125  1.00  1.00 | 116/110  0.93 (0.65-1.32)  0.87 (0.60-1.26) | 100/103  0.85 (0.58-1.24)  0.81 (0.55-1.20) | 76/93  0.71 (0.47-1.07)  0.66 (0.43-1.01) | | 0.10  0.06 |
| Anti-Flic-IgG, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 431/431  0.92 (0.80-1.07)  0.91 (0.78-1.06) | | 109/96  1.00  1.00 | 107/118  0.80 (0.55-1.17)  0.88 (0.59-1.30) | 104/105  0.86 (0.58-1.29)  0.93 (0.61-1.42) | 111/112  0.87 (0.59-1.29)  0.89 (0.59-1.34) | | 0.61  0.67 |
| Anti-LPS-IgA, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 431/431  0.86 (0.74-1.00)  0.85 (0.72-0.99) | | 134/119  1.00  1.00 | 125/103  1.05 (0.71-1.53)  1.04 (0.69-1.56) | 78/101  0.66 (0.44-0.99)  0.61 (0.40-0.94) | 94/108  0.72 (0.48-1.08)  0.70 (0.46-1.07) | | 0.03  0.02 |
| Anti-LPS-IgG, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-Flic, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-LPS, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb Total-Anti-Flic & LPS, no. Ca/Co  Matching-adjusted Modelᵃ  Fully-adjusted Modelb | | 431/431  0.91 (0.79-1.05)  0.89 (0.76-1.03)  431/431  0.89 (0.76-1.04)  0.87 (0.74-1.02)  431/431  0.86 (0.74-0.99)  0.84 (0.72-0.98)  431/431  0.86 (0.74-0.99)  0.83 (0.71-0.97) | | 119/114  1.00  1.00  118/102  1.00  1.00  130/119  1.00  1.00  127/103  1.00  1.00 | 101/98  0.98 (0.66-1.45)  1.13 (0.74-1.71)  108/119  0.77 (0.53-1.13)  0.75 (0.51-1.12)  105/90  1.04 (0.71-1.54)  1.08 (0.72-1.63)  108/117  0.75 (0.52-1.08)  0.72 (0.49-1.07) | 119/105  1.06 (0.73-1.55)  1.05 (0.71-1.56)  107/107  0.86 (0.59-1.25)  0.87 (0.59-1.28)  105/107  0.89 (0.60-1.30)  0.86 (0.58-1.28)  106/102  0.84 (0.57-1.24)  0.85 (0.57-1.27) | 92/114  0.76 (0.51-1.13)  0.74 (0.48-1.12)  98/103  0.79 (0.52-1.20)  0.76 (0.49-1.19)  91/115  0.68 (0.45-1.02)  0.64 (0.41-0.98)  90/109  0.63 (0.42-0.96)  0.61 (0.39-0.94) | | 0.26  0.18  0.40  0.39  0.05  0.03  0.06  0.06 |

Abbreviation: OD = optical density; SD = standard deviation; OR = odds ratio; CI = confidence interval; Flic = flagellin;

Ca/Co = case/control; Total-Anti-Flic = anti-flagellin-IgA + anti-flagellin-IgG; Total-Anti-LPS = anti-LPS-IgA + anti-LPS-IgG; Total-Anti-Flic & LPS = anti-flagellin-IgA + anti-flagellin-IgG + anti-LPS-IgA + anti-LPS-IgG

ƗPtrend test was based on median values of each quartile

ᵃMatching-adjusted model based on logistic regression conditioned on matching factors (age, gender, administrative centre and date of blood collection)

ᵇBased on matching factors plus adjustments for established confounding factors (smoking, alcohol consumption, body mass index, weight circumference, physical activity, education, and total daily dietary energy consumption, fibre intake, fruits and vegetable intakes, meat and processed meat consumption)