

**Table 1 Characteristics of included studies for the association between social isolation and all-cause mortality**

| First author           | Year | Country                            | Sample size      | Age*<br>(years) | Follow-u<br>p† | Exposure assessment                                                              | Effect Size HR/RR<br>(95% CI)                                                                       | Adjustment¶                                               |
|------------------------|------|------------------------------------|------------------|-----------------|----------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Masashige Saito        | 2021 | Japan                              | 15 313           | ≥65             | 10 y           | social isolation scale                                                           | HR 1.30 (1.12 to 1.50)                                                                              | 1, 2, 5, 27, 30, 31, 32                                   |
| Masashige Saito        | 2021 | UK                                 | 5124             | ≥50             | 10 y           | social isolation scale                                                           | HR 2.05 (1.52 to 2.73)                                                                              | 1, 2, 5, 6, 27, 30, 31, 32,<br>33, 34                     |
| Carin Lennartsson      | 2021 | Sweden                             | M 475<br>F 686   | ≥69             | 5 y            | social isolation index                                                           | All HR 2.544 (1.585 to 4.084)<br>Male HR 2.773 (1.502 to 5.119)<br>Female HR 2.727 (1.229 to 6.053) | 1, 2, 4, 33, 39, 40, 41                                   |
| Ryo Naito              | 2021 | 20 countries in<br>five continents | 118 764          | 35–70           | 9 y            | social network index                                                             | HR 1.26 (1.17 to 1.36)                                                                              | 1, 2, 4, 10, 11, 15, 18,<br>23, 24, 30, 35, 36, 37,<br>38 |
| Mark Ward              | 2021 | Ireland                            | 6915             | ≥50             | 7 y            | social network index                                                             | All HR 1.43 (1.09 to 1.87)<br>Male HR 1.18 (0.79 to 1.75)<br>Female HR 1.66 (1.08 to 2.54)          | 2, 4, 15, 18, 24, 30, 41,<br>44, 64, 65, 66               |
| Yoosik Youm            | 2021 | Korean                             | M 289<br>F 390   | ≥60             | 5.61 y         | the levels of participation<br>in seven different social<br>activities           | HR 1.53 (0.82 to 2.84)                                                                              | 2, 4, 15, 17, 18, 24, 25,<br>27, 29, 50                   |
| Christopher L<br>Crowe | 2021 | US                                 | 11302            | 50 - 95         | 8 y            | a six-item scale                                                                 | HR 1.38 (1.21 to 1.58)                                                                              | 1, 2, 6, 42, 43                                           |
| Janine Gronewold       | 2020 | Germany                            | M 1934<br>F 2205 | 45–75           | 13.4 y         | social integration index                                                         | All HR 1.47 (1.09 to 1.97)<br>Male HR 2.45 (1.54 to 3.87)<br>Female HR 1.11 (0.77 to 1.62)          | 1, 2                                                      |
| Emiel O<br>Hoogendijk  | 2020 | Netherlands                        | 1333             | ≥65             | 22 y           | combining information on<br>partner status, social<br>support, and network size. | HR 1.06 (0.92 to 1.21)                                                                              | 1, 2, 4, 15, 18, 44                                       |
| Heather Gilmour        | 2020 | Canada                             | M 5,408          | ≥65             | 8-9 y          | eight community-                                                                 | Male HR 1.3 (1.1 to 1.5)                                                                            | 1, 4, 5, 18, 30, 68, 69                                   |

|                   |      |           |                       |                |         |                         |                                                                                                                                                                                    |                                                                         |
|-------------------|------|-----------|-----------------------|----------------|---------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
|                   |      |           | F 7,629               |                |         | related activities      | Female HR 1.4 (1.2 to 1.6)                                                                                                                                                         |                                                                         |
| Siiri-Liisi Kraav | 2020 | Finland   | M 2588                | 42–61          | 23.2 y  | social isolation scale  | Male HR 1.086 (1.024 to 1.153)                                                                                                                                                     | 1, 15, 18, 19, 24, 36, 41, 45, 54, 69, 70, 71, 72                       |
| Kassandra         | 2019 | US        | M 245554<br>F 334628  | ≥30            | 15 y    | social network index    | All HR 1.43 (1.36 to 1.50)<br>Black Male HR 2.34 (1.58 to 3.46)<br>White Male HR 1.60 (1.41 to 1.82)<br>Black Female HR 2.13 (1.44 to 3.15)<br>White Female HR 1.84 (1.68 to 2.01) | 1, 2, 4, 6, 10, 18, 19                                                  |
| Ryota Sakurai     | 2019 | Japan     | M 417<br>F 606        | ≥65            | 6 y     | questionnaire           | HR 1.34 (0.64 to 2.81)                                                                                                                                                             | 1, 2, 4, 15, 27, 28, 29, 30                                             |
| Samuel G Smith    | 2018 | UK        | M 3007<br>F 3763      | ≥50            | 7.7 y   | social isolation index  | HR 1.29 (1.10 to 1.51)                                                                                                                                                             | 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 14, 15, 18, 20, 21, 22, 23, 24, 25, 26 |
| Johannes Beller   | 2018 | Germany   | Total 4838            | ≥40            | 20.83 y | social isolation score  | HR 1.21 (1.00 to 1.46)                                                                                                                                                             | 1, 2, 4, 5, 17, 44                                                      |
| Kristina Laugesen | 2018 | Denmark   | M 10119<br>F 11485    | 25-79          | 7 y     | social network index    | Male RR 1.7 (1.1 to 2.6)<br>Female RR 1.6 (0.83 to 2.9)                                                                                                                            | 1, 4, 18, 19, 23, 24, 27, 28, 33, 74, 75                                |
| Marko Elovainio   | 2017 | UK        | M 254919<br>F 211 982 | 40 - 69        | 6.5 y   | social isolation scale  | HR 1.26 (1.20 to 1.33)                                                                                                                                                             | 1, 2, 3, 4, 6, 15, 18, 19, 24, 25, 27, 32, 33, 44, 45, 46               |
| Chan, Angelique   | 2015 | Singapore | 4522                  | ≥60            | 1,459 d | social network scale    | HR 1.28 (0.90 to 1.82)                                                                                                                                                             | 1, 2, 4, 5, 6, 15, 18, 25, 32, 67                                       |
| Yang Claire Yang  | 2013 | US        | M 3082<br>F 3647      | ≥40            | 18 y    | social network index    | Male HR 1.53 (1.26 to 1.87)<br>Female HR 1.45 (1.20 to 1.75)                                                                                                                       | 1, 4, 6, 18, 19, 24, 27, 33, 44, 62                                     |
| Jorunn Drageset   | 2013 | Norway    | M 63<br>F 164         | ≥65            | 5 y     | social provisions scale | HR 1.02 (0.96 to 1.08)                                                                                                                                                             | 1, 2, 4, 5, 15, 49, 50, 51, 52, 53                                      |
| Matthew Pantell   | 2013 | US        | M 7875<br>F 8974      | 25-89,<br>> 89 | 14.1 y  | social network index    | Male HR 1.62 (1.29 to 2.02)<br>Female HR 1.75 (1.38 to 2.23)                                                                                                                       | 1, 4, 6, 27, 68, 73                                                     |

|                   |      |         |                    |                    |        |                              |                                                                                                                                                                |                                                               |
|-------------------|------|---------|--------------------|--------------------|--------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Masashige Saito   | 2012 | Japan   | M 6508<br>F 6802   | ≥65                | 4 y    | two items                    | All HR 1.19 (1.02 to 1.39)<br>Male HR 1.02 (0.85 to 1.24)<br>Female HR 1.72 (1.31 to 2.25)                                                                     | 1, 4, 5, 30, 38                                               |
| R.S. Tilvis       | 2012 | Finland | M 1187<br>F 2671   | > 75               | 7 y    | six questions                | Male HR 1.03 (0.87 to 1.23)<br>Female HR 1.00 (0.87 to 1.15)                                                                                                   | 1                                                             |
| Silvia Stringhini | 2012 | UK      | M 6,339<br>F 2,994 | 35–55              | 24.4 y | social network score         | Male HR 1.18 (0.99 to 1.40 )<br>Female HR 1.18 (0.90 to 1.53)                                                                                                  | 1, 4, 20, 27, 33                                              |
| Lisa F Berkman    | 2004 | French  | M 12347<br>F 4352  | M 40-50<br>F 35-50 | 8 y    | social integration index     | Male RR 2.70 (1.17 to 6.23)<br>Female RR 3.64 (0.72 to 18.58)                                                                                                  | 1, 15, 18, 19, 20, 24, 30, 33                                 |
| Brenda K Keller   | 2003 | US      | M 370<br>F 900     | 49-97              | 10 y   | social network index         | HR 1.25 (0.97 to 1.61)                                                                                                                                         | 1, 4, 27, 32, 47, 48                                          |
| Patricia M. Eng   | 2002 | US      | M 28369            | 42–77              | 10 y   | social network index         | Male RR 1.20 (0.97 to 1.48)                                                                                                                                    | 1, 8, 10, 13, 16, 18, 19, 20, 24, 37, 41, 54, 69              |
| Tom K. Greenfield | 2002 | US      | M 2031<br>F 3062   | ≥18                | 11 y   | social isolation scale       | Male RR 0.99 (0.71 to 1.39)<br>Female RR 0.83 (0.56 to 1.22)                                                                                                   | 1, 5, 6, 17, 18, 24, 27                                       |
| Heiner Maier      | 1999 | Germany | M 257<br>F 256     | 70-103             | 6 y    | loneliness scale             | RR 1.11(0.99-1.25)                                                                                                                                             | unadjusted                                                    |
| T E Seeman        | 1993 | US      | M 1431<br>F 2330   | ≥65                | 5 y    | four measures of social ties | Male HR 0.99 (0.66 to 1.51)<br>Female HR 1.28 (0.79 to 2.03)                                                                                                   | 1, 18, 19, 25, 38, 41, 44, 69                                 |
| T E Seeman        | 1993 | US      | M 1150<br>F 1936   | ≥65                | 5 y    | four measures of social ties | Male HR 1.42 (0.87 to 2.32)<br>Female HR 1.89 (1.18 to 3.04)                                                                                                   | 1, 18, 19, 25, 38, 41, 44, 69                                 |
| T E Seeman        | 1993 | US      | M 1150<br>F 1618   | ≥65                | 5 y    | four measures of social ties | Male HR 2.40 (1.35 to 3.07)<br>Female HR 1.78 (1.05 to 3.03)                                                                                                   | 1, 18, 19, 25, 38, 41, 44, 69                                 |
| V J Schoenbach    | 1986 | US      | 2059               | 54.1               | 12 y   | social network index         | White HR 1.5 (1.0 to 2.2)<br>Black HR 1.4 (0.8 to 2.3)<br>White Male HR 1.5 (0.8 to 2.6)<br>White Female HR 1.3 (0.7 to 2.3)<br>Black Male HR 1.3 (0.6 to 2.7) | 1, 10, 18, 41, 42, 45, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 |

|                     |      |         |       |       |     |                |                                                                 |                                 |
|---------------------|------|---------|-------|-------|-----|----------------|-----------------------------------------------------------------|---------------------------------|
| GEORGE A.<br>KAPLAN | 1988 | Finland | 13301 | 39-59 | 5 y | five questions | Black Female HR 1.1 (0.5 to 2.6)<br>Male OR 2.00 (1.18 to 3.39) | 1, 4, 18, 19, 30, 41, 45,<br>54 |
|---------------------|------|---------|-------|-------|-----|----------------|-----------------------------------------------------------------|---------------------------------|

HR=hazard ratio; RR=relative risk; 95%CI=95%Confidence interval; M=Male; F=Female.

\*Presented as mean or range.

†Number of years that individuals were followed up in the prospective cohort studies.

¶Adjustments: age (1), sex (2), wealth (3), education (4), marital status (5), ethnicity (6), long-standing illness (7), time period (8), cancer (9), diabetes (10), coronary heart disease (CHD) (11), chronic lung disease (12), intakes of total fat, saturated fat, folate, and fiber (13), stroke (14), diagnosed depression (15), multivitamin and vitamin E supplement use (16), loneliness (17), smoking status (18), body mass index (19), occupational class (20), functional impairment (21), asthma (22), exercise (23), drinking (24), cognitive function (25), health literacy (26), income level (27), comorbidities (28), subjective health (29), residential areas (30), presence of medical treatment (31), basic activities of daily living (ADL) (32), self-rated health (33), household size (34), country income (LIC, MIC or HIC) (35), diet score (36), hypertension (37), disabilities (38), mobility limitations (39), psychological distress (40), problems related to cardiovascular diseases (41), age-squared (42), age-sex interactions (43), chronic disease (44), diastolic and systolic blood pressure (45), handgrip strength (46), cumulative illness rating scale (CIRS) (47), informal service use (48), length of stay (49), comorbidity (50), attachment (51), reassurance of worth (52), nurturance (53), serum cholesterol (54), serum cholesterol squared (55), Electrocardiographic abnormality (56), electrocardiographic abnormality (57), quetelet index (58), quetelet index squared (59), social class (60), social class squared (61), off-job physical activity (62), off-job physical activity squared (63), walk minutes (64), obese (65), polypharmacy (66), housing type (67), health status (68), physical activity (69), hours slept at night (70), High-sensitivity C-reactive protein( hs-CRP) (71), low-density lipoprotein cholesterol (72), clinical risk factor (73), past or present use of antidepressants (74), past or present use of strong analgesics (75).

**Table 2 Characteristics of included studies for the association between social isolation and cardiovascular disease or circulatory system diseases mortality**

| First author      | Year | Country                         | Sample size           | Age* (years) | Follow-up† | Exposure assessment    | Events for analysis                   | Effect Size HR/RR/OR (95% CI)                                                                                                                        | Adjustment¶                                              |
|-------------------|------|---------------------------------|-----------------------|--------------|------------|------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Ryo Naito         | 2021 | 20 countries in five continents | 118 764               | 35–70        | 9 y        | social network index   | cardiovascular disease mortality      | HR 1.30 (1.13 to 1.50)                                                                                                                               | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14            |
| Mark Ward         | 2021 | Ireland                         | 6915                  | ≥50          | 7 y        | social network index   | circulatory system diseases mortality | All HR 1.19 (0.75 to 1.88)<br>Male HR 1.54 (0.90 to 2.63)<br>Female HR 0.77 (0.35 to 1.70)                                                           | 2, 3, 4, 6, 7, 13, 16, 24, 25, 26                        |
| Siiri-Liisi Kraav | 2020 | Finland                         | M 2588                | 42–61        | 23.2 y     | social isolation scale | cardiovascular disease mortality      | Male HR 1.063 (0.974 to 1.159)                                                                                                                       | 6, 7, 8, 9, 13, 17, 18, 27, 29, 30, 31, 33               |
| Kassandra         | 2019 | US                              | M 245554<br>F 334628  | ≥30          | 15 y       | social network index   | cardiovascular disease mortality      | Black Male HR 1.51 (1.16 to 1.97)<br>White Male HR 1.29 (1.21 to 1.38)<br>Black Female HR 1.49 (1.14 to 1.96)<br>White Female HR 1.47 (1.37 to 1.57) | 1, 2, 3, 6, 11, 15, 17                                   |
| Marko Elovainio   | 2017 | UK                              | M 254919<br>F 211 982 | 40 - 69      | 6.5 y      | social isolation scale | circulatory system diseases mortality | HR 1.24 (1.17 to 1.31)                                                                                                                               | 1, 2, 3, 6, 7, 8, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23 |
| Yang Claire Yang  | 2013 | US                              | M 3082<br>F 3647      | ≥40          | 18 y       | social network index   | circulatory system diseases mortality | Male HR 1.56 (1.16 to 2.10)<br>Female HR 1.47 (1.11 to 1.95)                                                                                         | 1, 3, 6, 7, 8, 15, 16, 17, 21, 34                        |
| Silvia Stringhini | 2012 | UK                              | M 6,339<br>F 2,994    | 35–55        | 24.4 y     | social network score   | cardiovascular disease mortality      | Male HR 1.66 (1.22 to 2.26)<br>Female HR 1.4 (0.77 to 1.54)                                                                                          | 1, 3, 29, 34                                             |
| Kathi L. Heffner  | 2011 | US                              | 327                   | ≥40          | 15 y       | social integration     | coronary heart disease mortality      | OR 2.66 (1.03 to 6.85)                                                                                                                               | 1, 2, 27, 28                                             |

|                  |      |         |                   |                     |      |                                         |                                     |                              |                                                                      |
|------------------|------|---------|-------------------|---------------------|------|-----------------------------------------|-------------------------------------|------------------------------|----------------------------------------------------------------------|
| Lisa F Berkman   | 2004 | French  | M 12347<br>F 4352 | M;40-50<br>F: 35-50 | 8 y  | index<br>social<br>integration<br>index | cardiovascular<br>disease mortality | Male RR 1.29 (0.16 to 10.41) | 1, 4, 6, 7, 13, 17, 23,<br>36                                        |
| Patricia M. Eng  | 2002 | US      | M 28369           | 42–77               | 10 y | social network<br>index                 | cardiovascular<br>disease mortality | Male RR 1.37 (0.91 to 2.08)  | 1, 6, 7, 8, 10, 11, 17,<br>32, 35, 36, 37, 38, 39,<br>40, 41, 42, 43 |
| GEORGE A. KAPLAN | 1988 | Finland | 13301             | 39-59               | 5 y  | five questions                          | cardiovascular<br>disease mortality | Male OR 1.8 (0.87 to 3.72)   | 1, 3, 4, 6, 17, 18, 32,<br>33, 44                                    |
| GEORGE A. KAPLAN | 1988 | Finland | 13301             | 39-59               | 5 y  | five questions                          | ischemic heart<br>disease mortality | Male OR 1.72 (0.77 to 3.84)  | 1, 3, 4, 6, 17, 18, 32,<br>33, 44                                    |

HR=hazard ratio; RR=relative risk; OR=odds ratio; 95%CI=95%Confidence interval; M= Male; F= Female.

\*Presented as mean or range.

†Number of years that individuals were followed up in the prospective cohort studies.

¶Adjustments: age (1), sex (2), education (3), residence area (4), country income (5), smoking (6), alcohol use (7), physical inactivity (8), diet score (9), hypertension (10), diabetes (11), coronary artery disease (12), depression (13), disabilities (14). Ethnic (15), chronic disease (16), body mass index (BMI) (17), diastolic and systolic blood pressure (18), a handgrip strength (19), Townsend deprivation index (20), household income (21), cognitive performance (22), self-rated health (23), walk minutes (24), obese (25), polypharmacy (26), C-reactive protein (CRP) (27), Framingham risk category (28), adulthood socioeconomic status (29), hours slept at night (30), low-density lipoprotein cholesterol (31), cholesterol (32), past history of cardiovascular disease (33), self-rated health (34), time period (35), occupation (36), routine physical examination (37), ability to climb several flights of stairs (38), ability to do heavy housework (39), employment status (40), history of myocardial infarction in a parent (41), total fat, saturated fat, folate, and fiber (42), multivitamin and vitamin E supplement use (43), province (44).

**Table 3 Characteristics of included studies for the association between social isolation and cancer mortality**

| First author          | Year | Country | Sample size           | Age* (years)       | Follow-up† | Exposure assessment      | Effect Size HR/RR (95% CI)                                                                                                                                                         | Adjustment‡                                            |
|-----------------------|------|---------|-----------------------|--------------------|------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Mark Ward             | 2021 | Ireland | 6915                  | ≥50                | 7 y        | social network index     | All HR 1.18 (0.82 to 1.69)<br>Male HR 0.89 (0.55 to 1.43)<br>Female HR 1.43 (0.78 to 2.65)                                                                                         | 2, 5, 6, 7, 8, 9, 18, 19, 20, 21, 22                   |
| Laura C Pinheiro      | 2021 | US      | 29766                 | ≥45                | 10.6 y     | one question             | HR 1.20 (0.99 to 1.44)                                                                                                                                                             | 1, 2                                                   |
| Alexander Koh-Bell    | 2021 | US      | F 3360                | ≥40                | 6y         | social network index     | Female HR 0.76 (0.28 to 2.06)                                                                                                                                                      | 3, 5, 7, 8, 11, 14, 16, 17, 21, 23, 27, 40, 41         |
| Siiri-Liisi Kraav     | 2020 | Finland | M 2588                | 42–61              | 23.2 y     | social isolation scale   | Male HR 1.073 (0.955 to 1.206)                                                                                                                                                     | 1, 7, 8, 9, 11, 12, 14, 21, 24, 25, 26, 27, 28         |
| Kassandra             | 2019 | US      | M 245554<br>F 334628  | ≥30                | 15 y       | social network index     | All HR 1.43 (1.36 to 1.50)<br>Black Male HR 1.07 (0.77 to 1.49)<br>White Male HR 1.25 (1.17 to 1.34)<br>Black Female HR 0.94 (0.68 to 1.30)<br>White Female HR 1.26 (1.17 to 1.36) | 1, 2, 3, 5, 7, 11, 23                                  |
| Andrea Fleisch Marcus | 2017 | US      | M 6989<br>F 8146      | ≥18                | 23 y       | social network index     | All HR 1.15 (0.92 to 1.43)<br>Male HR 1.13 (0.85 to 1.50)<br>Female HR 1.23 (0.87 to 1.73)                                                                                         | 1, 2, 3, 4, 5                                          |
| Marko Elovainio       | 2017 | UK      | M 254919<br>F 211 982 | 40 - 69            | 6.5 y      | social isolation scale   | HR 1.32 (1.22 to 1.43)                                                                                                                                                             | 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 |
| Yang Claire Yang      | 2013 | US      | M 3082<br>F 3647      | ≥40                | 18 y       | social network index     | Male HR 1.30 (0.87 to 1.95)<br>Female HR 0.86 (0.55 to 1.34)                                                                                                                       | 1, 3, 5, 6, 7, 8, 11, 16, 17                           |
| Lisa F Berkman        | 2004 | French  | M 12347<br>F 4352     | M 40-50<br>F 35-50 | 8 y        | social integration index | Male RR 3.60 (0.99 to 13.01)                                                                                                                                                       | 1, 7, 8, 9, 11, 17, 30, 39                             |

|                 |      |    |         |       |      |                      |                             |                                                                |
|-----------------|------|----|---------|-------|------|----------------------|-----------------------------|----------------------------------------------------------------|
| Patricia M. Eng | 2002 | US | M 28369 | 42–77 | 10 y | social network index | Male RR 0.86 (0.59 to 1.25) | 1, 7, 8, 11, 14, 23, 29, 30, 31,<br>32, 33, 34, 35, 36, 37, 38 |
|-----------------|------|----|---------|-------|------|----------------------|-----------------------------|----------------------------------------------------------------|

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HR=hazard ratio; RR=risk ratio; 95%CI=95%Confidence interval; M=Male; F=Female.

\*Presented as mean or range.

†Number of years that individuals were followed up in the prospective cohort studies.

‡Adjustments: age (1), sex (2), ethnicity (3), poverty income ratio (4), education (5), chronic disease (6), smoking (7), alcohol consumption (8), depressive symptoms (9), cognitive performance (10), body mass index (BMI) (11), diastolic and systolic blood pressure (12), handgrip strength (13), physical activity (14), townsend deprivation index (15), household income (16), self-rated health (17), urban (18), walk minutes (19), obese (20), cardiovascular disease (CVD) (21), polypharmacy (22), diabetes (23), adulthood socioeconomic status (24), diet score (25), hours slept at night (26), high-sensitivity C-reactive protein (hs-CRP) (27), low-density lipoprotein cholesterol (28), time period (29), occupation (30), routine physical examination (31), ability to climb several flights of stairs (32), ability to do heavy housework (33), employment status (34), hypertension (35), history of myocardial infarction in a parent aged <60 years (36), intake of total fat, saturated fat, folate, and fiber (37), multivitamin and vitamin E supplement use (38), geographic region (39), non-steroidal anti-inflammatory drug use (40), fibrinogen (41).