SUPPLEMENTAL MATERIAL
| Section/topic | # | Checklist item                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------|-------------------|
| Title         |   | Identify the report as a systematic review, meta-analysis, or both.             | 1                 |
| Abstract      |   | Provide a structured summary including, as applicable: background; objectives;  | 2-3               |
|               |   | data sources; study eligibility criteria, participants, and interventions;     |                   |
|               |   | study appraisal and synthesis methods; results; limitations; conclusions and   |                   |
|               |   | implications of key findings; systematic review registration number.           |                   |
| Introduction  |   | Describe the rationale for the review in the context of what is already known. | 4-5               |
| Methods       |   | Provide an explicit statement of questions being addressed with reference to   | 5                 |
|               |   | participants, interventions, comparisons, outcomes, and study design (PICOS).  |                   |
| Protocol and  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g.,   |                   |
| registration  |   | Web address), and, if available, provide registration information including     |                   |
|               |   | registration number.                                                          |                   |
| Eligibility   | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report    | 5                 |
| criteria      |   | characteristics (e.g., years considered, language, publication status) used    |                   |
|               |   | as criteria for eligibility, giving rationale.                                 |                   |
| Information   | 7 | Describe all information sources (e.g., databases with dates of coverage,     | 5-6               |
| sources       |   | contact with study authors to identify additional studies) in the search and   |                   |
|               |   | date last searched.                                                            |                   |
| Search        | 8 | Present full electronic search strategy for at least one database, including   | 5                 |
|               |   | any limits used, such that it could be repeated.                               |                   |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included | 6                 |
|               |   | in systematic review, and, if applicable, included in the meta-analysis).     |                   |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms,          | 6                 |
|               |   | independently, in duplicate) and any processes for obtaining and confirming    |                   |
|               |   | data from investigators.                                                       |                   |
| Data items    | 11| List and define all variables for which data were sought (e.g., PICOS, funding | 6                 |
|               |   | sources) and any assumptions and simplifications made.                         |                   |
| Risk of bias  | 12| Describe methods used for assessing risk of bias of individual studies (including| 6-7               |
| in individual |   | specification of whether this | |
| Studies                        | was done at the study or outcome level), and how this information is to be used in any data synthesis. |
|--------------------------------|------------------------------------------------------------------------------------------------------|
| Summary measures               | State the principal summary measures (e.g., risk ratio, difference in means).                        |
| Synthesis of results           | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. |
| Risk of bias across studies    | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| Additional analyses            | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |

### Results

| Study selection                | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| Study characteristics          | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| Risk of bias within studies    | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| Results of individual studies  | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| Synthesis of results           | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| Risk of bias across studies    | Present results of any assessment of risk of bias across studies (see Item 15). |
| Additional analysis            | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |

### Discussion

| Summary of evidence            | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |
| Limitations                    | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| Conclusions                    | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |

### Funding

| Funding                        | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |
### Table S2. Outcome definitions

| Study  | CVD        | CHD        | Stroke      | fatal CVD   |
|--------|------------|------------|-------------|-------------|
| 45&Up  | I20-I25, I61-I67, I69 | -          | -           | I20-I25, I61-I67, I69 |
| CKB    | I00-I99 (fatal), I20-I25, I60-I69 | I20-I25 | I60-I69 | I00-I99 |
| EPIC   | I00-I99 | I20-I25 | I60-I69 | I00-I99 |
| Gallagher | 410-414, 421, 434 | 410-414 | 431, 434 | 410-414, 421, 434 |
| HUNT2  | I00-I99 | -         | -           | I00-I99 |
| JPHC   | I20-I52, I60-I69 | I20-I52 | I60-I69 | I20-I52, I60-I69 |
| NHS    | -         | MI or fatal CHD | -         | -         |
| WHI    | CHD, stroke, CHF, angina, PVD, MI, fatal CHD, ischemic or CAD, or coronary revascularization | CABG, or PTCA hemorrhagic stroke | - |

Codes correspond to the International Classification of Diseases (ICD) version 9 or 10. Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CHF, chronic heart failure; CVD, cardiovascular disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Full study names are provided in the footnote of **Table 1**.
**Table S3. Variables in the adjustment of the primary analysis.**

| Study acronym | 45&Up | CKB | EPIC | Gallagher | HUNT2 | JPHC | NHS | WHI |
|---------------|-------|-----|------|-----------|-------|------|-----|-----|
| [Ref]         | [7]   | [8] | [9]  | [10]      | [11]  | [12] | [13]| [14]|

**Demographics**
- Age
- Country of birth/ethnicity
- Study center/area
- Extension study inclusion
- Socioeconomic status
  - Socioeconomic status score
  - Income
  - Education
  - Job status
  - Living arrangement
  - Marital status

**Cardiovascular risk factors**
- Body mass index
- Birthweight of subject
- Smoking status/history/duration
- Alcohol intake
- Systolic blood pressure
- History of hypertension/antihypertensive treatment
- History of diabetes/antidiabetic treatment
- Aspirin use
- Total cholesterol
- High-density lipoprotein cholesterol
- Dyslipidemia
- Omega 3 fatty acid use
- Multivitamin use
- Diet
- Physical activity
- Family history of CVD/diabetes/hypertension

**Reproductive factors**
- Parity
- Number of livebirths
- History/number of stillbirth/s
- Number of miscarriages
- Age at first child
- Age at last child
- Age at menarche
- Age at menopause
- Menopausal status
- Total fertility span
- Hormone intake

**Level of adjustment**

- +, adjusted for demographics and cardiovascular risk factors
- ++, adjusted for demographics, reproductive factors, and cardiovascular risk factors

Abbreviations: CVD, cardiovascular disease. Full study names are provided in the footnote of Table 1.
Table S4. GRADE summary of findings.

| Certainty assessment | CVD | CHD | Stroke | Fatal CVD |
|----------------------|-----|-----|--------|-----------|
| No. of studies       | 7   | 6   | 5      | 6         |
| Study design         | observational studies | observational studies | observational studies | observational studies |
| Risk of bias         | not serious | not serious | not serious | not serious |
| Inconsistency        | very serious ($I^2=79.4\%$) | very serious ($I^2=79.7\%$) | very serious ($I^2=79.6\%$) | not serious |
| Indirectness         | not serious | not serious | not serious | not serious |
| Imprecision          | not serious | not serious | not serious | not serious |
| Other considerations | publication bias strongly suspected ($P_{	ext{Egger}}=0.003$), dose response gradient | dose response gradient | dose response gradient | dose response gradient |
| Relative effect (95% CI) | HR 0.89 (0.83-0.95) | HR 0.86 (0.78-0.95) | HR 0.88 (0.79-0.99) | HR 0.83 (0.76-0.92) |
| Certainty            | VERY LOW | VERY LOW | VERY LOW | MODERATE |

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio.
Figure S1. Funnel plots for each cardiovascular outcome.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease. Full study names are provided in the footnote of Table 1.
Figure S2. Subgroup analyses according to mean age at baseline, median duration of follow-up, and mean parity.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease. Sizes of the circles are proportional to the variance of the effect estimates. Solid lines indicate fitted meta-regression lines and shaded areas their 95% confidence interval. P-values are derived from meta-regression.
Figure S3. Subgroup analyses according to level of adjustment and Newcastle-Ottawa Scale.

| Subgroup     | No. of studies | No. of parous women | Hazard ratio (95% CI) | P value* |
|--------------|----------------|---------------------|-----------------------|----------|
| **CVD**      |                |                     |                       |          |
| Adjustment   |                |                     |                       |          |
| ○            | 1              | 254,116             | 0.92 (0.86, 0.99)     | 0.782    |
| +            | 1              | 285,603             | 0.91 (0.86, 0.97)     |          |
| ++           | 5              | 563,655             | 0.85 (0.75, 0.97)     |          |
| **NOS**      |                |                     |                       |          |
| ≤6           | 1              | 254,116             | 0.92 (0.86, 0.99)     | 0.647    |
| >6           | 6              | 849,258             | 0.87 (0.80, 0.95)     |          |
| **Region**   |                |                     |                       |          |
| Asia         | 3              | 577,215             | 0.91 (0.87, 0.95)     | 0.697    |
| Other        | 4              | 526,159             | 0.85 (0.73, 0.99)     |          |
| **CHD**      |                |                     |                       |          |
| Adjustment   |                |                     |                       |          |
| ○            | 1              | 254,116             | 0.64 (0.54, 0.76)     | 0.110    |
| +            | 1              | 285,603             | 0.91 (0.83, 0.99)     |          |
| ++           | 4              | 197,293             | 0.92 (0.85, 0.99)     |          |
| **NOS**      |                |                     |                       |          |
| ≤6           | 2              | 343,442             | 0.80 (0.53, 1.20)     | 0.672    |
| >6           | 4              | 393,570             | 0.90 (0.85, 0.94)     |          |
| **Region**   |                |                     |                       |          |
| Asia         | 3              | 577,215             | 0.80 (0.64, 1.01)     | 0.508    |
| Other        | 3              | 159,797             | 0.92 (0.84, 1.00)     |          |
| **Stroke**   |                |                     |                       |          |
| Adjustment   |                |                     |                       |          |
| ○            | 1              | 254,116             | 1.00 (0.92, 1.08)     | 0.141    |
| +            | 1              | 285,603             | 0.92 (0.85, 0.99)     |          |
| ++           | 3              | 384,294             | 0.79 (0.72, 0.87)     |          |
| **NOS**      |                |                     |                       |          |
| ≤6           | 2              | 334,307             | 0.88 (0.68, 1.13)     | 0.946    |
| >6           | 3              | 589,706             | 0.91 (0.85, 0.97)     |          |
| **Region**   |                |                     |                       |          |
| Asia         | 3              | 577,215             | 0.93 (0.85, 1.03)     | 0.266    |
| Other        | 2              | 346,798             | 0.82 (0.68, 0.99)     |          |
| **Fatal CVD**|               |                     |                       |          |
| Adjustment   |                |                     |                       |          |
| ○            | 1              | 254,116             | 0.92 (0.86, 0.99)     | 0.167    |
| +            | 1              | 285,603             | 0.90 (0.69, 1.17)     |          |
| ++           | 4              | 424,974             | 0.79 (0.72, 0.86)     |          |
| **NOS**      |                |                     |                       |          |
| ≤6           | 1              | 254,116             | 0.92 (0.86, 0.99)     | 0.071    |
| >6           | 5              | 710,577             | 0.80 (0.73, 0.87)     |          |
| **Region**   |                |                     |                       |          |
| Asia         | 3              | 577,215             | 0.90 (0.85, 0.96)     | 0.063    |
| Other        | 3              | 387,478             | 0.76 (0.68, 0.86)     |          |

○, adjusted for demographics and reproductive factors; +, adjusted for demographics and cardiovascular risk factors; ++, adjusted for demographics, reproductive factors, and cardiovascular risk factors. *P value for heterogeneity. Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; NOS, Newcastle-Ottawa Scale.
Figure S4. Leave-one-out meta-analysis for each cardiovascular outcome.

| Outcome/omitted study | Hazard ratio (95% CI) | $I^2$ (95% CI), % |
|-----------------------|-----------------------|-------------------|
| **CVD**               |                       |                   |
| 45&Up                 | 0.90 (0.83, 0.96)     | 77.9 (51.2, 90.0) |
| CKB                   | 0.87 (0.80, 0.96)     | 81.8 (61.3, 91.5) |
| EPIC                  | 0.90 (0.84, 0.97)     | 77.9 (51.2, 90.0) |
| Gallagher             | 0.87 (0.80, 0.95)     | 82.4 (62.8, 91.7) |
| HUNT2                 | 0.90 (0.84, 0.96)     | 80.3 (57.4, 90.9) |
| JPHC                  | 0.89 (0.83, 0.96)     | 81.3 (59.8, 91.3) |
| WHI                   | 0.87 (0.82, 0.92)     | 43.9 (0.0, 77.8)  |
| **No study omitted**  | **0.89 (0.83, 0.95)** | **79.4 (57.8, 89.9)** |
| **CHD**               |                       |                   |
| CKB                   | 0.84 (0.74, 0.95)     | 83.8 (63.3, 92.8) |
| EPIC                  | 0.87 (0.79, 0.96)     | 82.0 (58.5, 92.2) |
| Gallagher             | 0.92 (0.87, 0.97)     | 38.9 (0.0, 77.3)  |
| JPHC                  | 0.85 (0.77, 0.95)     | 83.7 (63.1, 92.8) |
| NHS                   | 0.82 (0.73, 0.93)     | 76.3 (42.1, 90.3) |
| WHI                   | 0.83 (0.72, 0.96)     | 83.6 (63.0, 92.8) |
| **No study omitted**  | **0.86 (0.78, 0.95)** | **79.7 (55.8, 90.7)** |
| **Stroke**            |                       |                   |
| CKB                   | 0.87 (0.74, 1.03)     | 84.3 (60.5, 93.7) |
| EPIC                  | 0.88 (0.77, 0.99)     | 84.6 (61.5, 93.8) |
| Gallagher             | 0.85 (0.75, 0.96)     | 68.8 (9.9, 89.2)  |
| JPHC                  | 0.90 (0.79, 1.02)     | 83.6 (58.4, 93.5) |
| WHI                   | 0.94 (0.87, 1.01)     | 36.7 (0.0, 78.2)  |
| **No study omitted**  | **0.88 (0.79, 0.99)** | **79.6 (51.6, 91.4)** |
| **Fatal CVD**         |                       |                   |
| 45&Up                 | 0.86 (0.79, 0.93)     | 35.4 (0.0, 75.8)  |
| CKB                   | 0.82 (0.73, 0.91)     | 57.9 (0.0, 84.3)  |
| EPIC                  | 0.84 (0.74, 0.94)     | 48.2 (0.0, 81.0)  |
| Gallagher             | 0.80 (0.73, 0.87)     | 0.0 (0.0, 79.2)   |
| HUNT2                 | 0.85 (0.77, 0.93)     | 46.4 (0.0, 80.3)  |
| JPHC                  | 0.82 (0.73, 0.93)     | 57.0 (0.0, 84.0)  |
| **No study omitted**  | **0.83 (0.76, 0.92)** | **47.7 (0.0, 79.3)** |

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease. Full study names are provided in the footnote of Table 1.