Supplementary Material

RELATION OF VEGETARIAN DIETARY PATTERNS WITH MAJOR CARDIOVASCULAR OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

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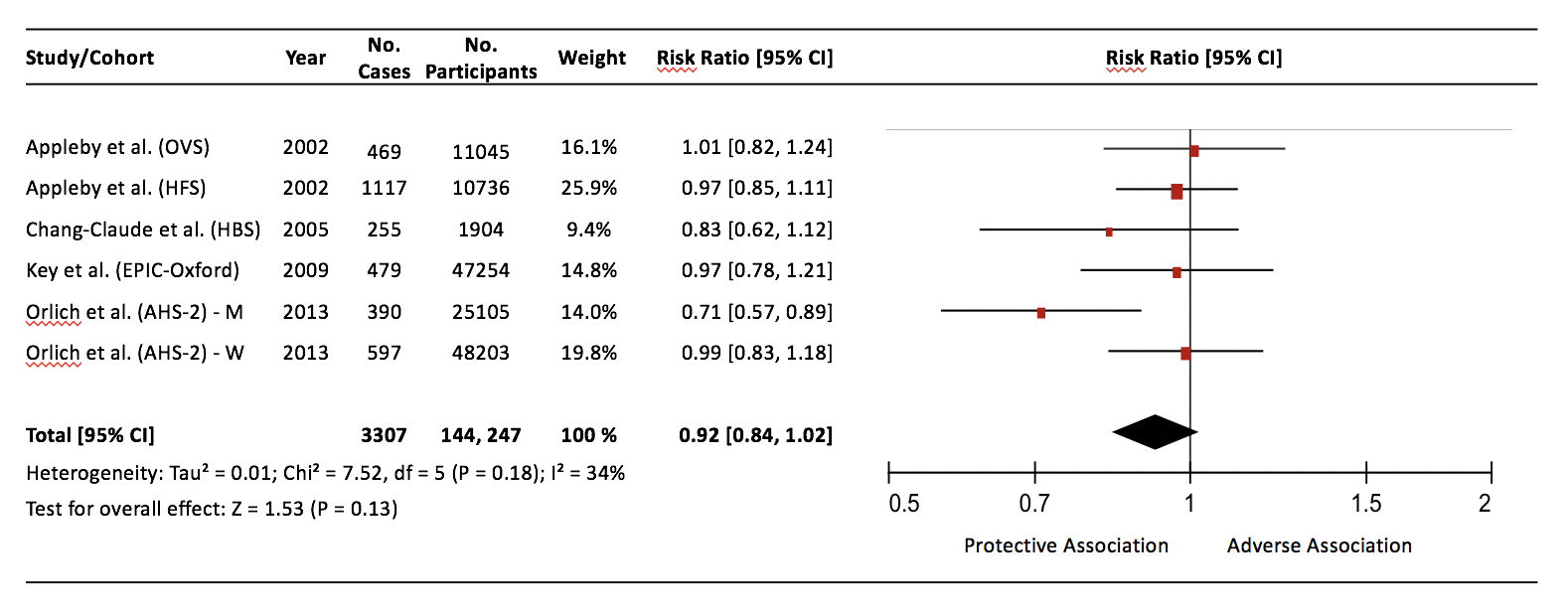
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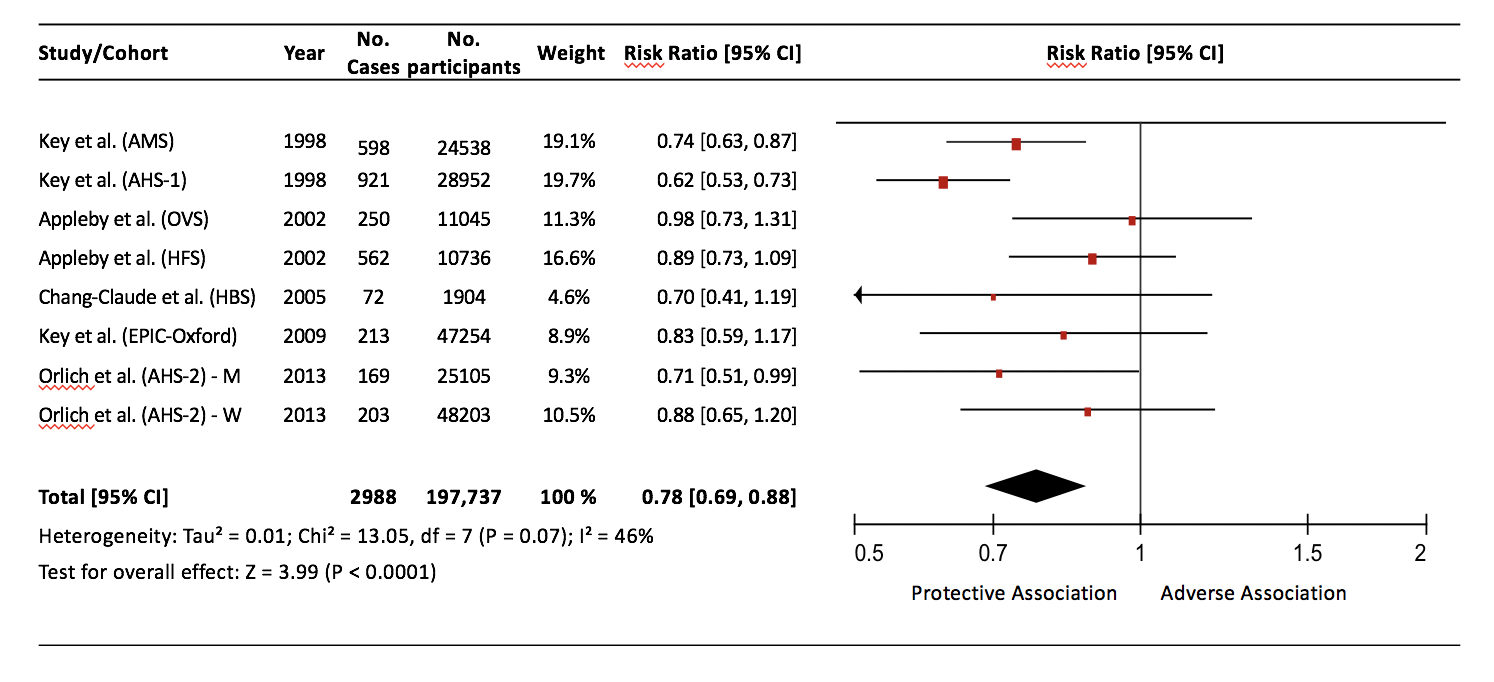
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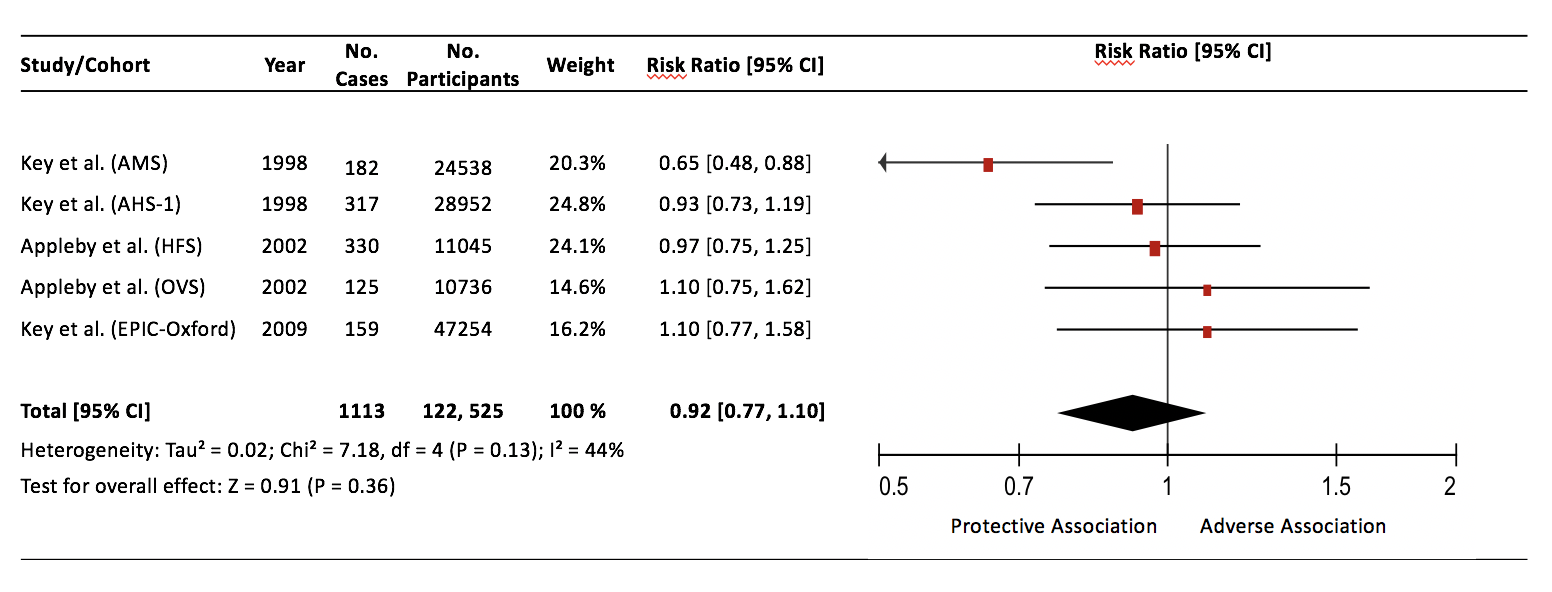
**Supplementary Figure 1.** Association between vegetarian dietary patterns and CVD mortality.

Pooled risk estimate is represented by the diamond. Values of I2≥50% indicate substantial heterogeneity (Guyatt et al., 2011e). Values greater than 1.0 indicate an adverse association. AHS-2=Adventist Health Study-2; CVD=cardiovascular disease; CI=confidence interval; EPIC=European Prospective Cohort into Cancer and Nutrition; HBS=Heidelberg Study; HFS=Health Food Shoppers; M=men; OVS=Oxford Vegetarian Study; W=women.



**Supplementary Figure 2.** Association between vegetarian dietary patterns and CHD mortality.

Pooled risk estimate is represented by the diamond. Values of I2≥50% indicate substantial heterogeneity (Guyatt et al., 2011e). Values greater than 1.0 indicate an adverse association. AHS-1=Adventist Health Study-1; AHS-2=Adventist Health Study-2; AMS=Adventist Mortality Study; CHD=coronary heart disease; CI=confidence interval; EPIC=European Prospective Cohort into Cancer and Nutrition; HBS=Heidelberg Study; HFS=Health Food Shoppers; M=men; OVS=Oxford Vegetarian Study; W=women.



Supplementary Figure 3. Association of vegetarian dietary patterns with stroke mortality

Pooled risk estimate is represented by the diamond. Values of I2≥50% indicate substantial heterogeneity (Guyatt et al., 2011e). Values greater than 1.0 indicate an adverse association. AHS-1=Adventist Health Study-1; AMS=Adventist Mortality Study; CI=confidence interval; EPIC=European Prospective Cohort into Cancer and Nutrition; HFS=Health Food Shoppers; OVS=Oxford Vegetarian Study.

**1.2 Supplementary Tables**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Medline**: November 1st, 2017.  Updated September 6th, 2018. | | **Embase**: November 1st, 2017.  Updated September 6th, 2018. | | **Cochrane**: November 1st, 2017.  Updated September 6th, 2018. | |
| 1 | plant-based diet\*.mp | 1 | plant-based diet\*.mp | 1 | plant-based diet\*.mp |
| 2 | (plant adj1 diet).mp | 2 | (plant adj1 diet).mp | 2 | (plant adj1 diet).mp |
| 3 | exp diet,vegetarian/ | 3 | exp vegetarian diet/ | 3 | exp diet,vegetarian/ |
| 4 | vegetarian\*.mp | 4 | exp vegetarian/ | 4 | vegetarian\*.mp |
| 5 | vegan\*.mp | 5 | vegetarian\*.mp | 5 | vegan\*.mp |
| 6 | lactoovo\*.mp | 6 | vegan\*.mp | 6 | lacto-ovo\*.mp |
| 7 | lacto-ovo\*.mp | 7 | lactoovo\*.mp | 7 | or/1-6 |
| 8 | ovolacto\*.mp | 8 | lacto-ovo\*.mp |  |  |
| 9 | ovo-lacto\*.mp | 9 | ovolacto\*.mp | 8 | cohort.mp. |
| 10 | or/1-9 | 10 | ovo-lacto\*.mp | 9 | exp Prospective Studies/ |
|  |  | 11 | or/1-10 | 10 | (prospective adj2 (cohort or study)).mp. |
| 11 | cohort.mp. |  |  | 11 | exp follow-up studies/ |
| 12 | exp prospective study/ | 12 | cohort.mp. | 12 | exp multivariate analysis/ |
| 13 | (prospective adj2 (cohort or study)).mp. | 13 | exp prospective study/ | 13 | exp proportional hazards models/ |
| 14 | exp follow-up studies/ | 14 | (prospective adj2 (cohort or study)).mp. | 14 | follow up study.mp. |
| 15 | exp multivariate analysis/ | 15 | exp multivariate analysis/ | 15 | (longitudinal adj2 study).mp. |
| 16 | exp proportional hazards models/ | 16 | exp proportional hazards models/ | 16 | or/8-15 |
| 17 | follow up study.mp. | 17 | follow up study.mp. |  |  |
| 18 | (longitudinal adj2 study).mp. | 18 | (longitudinal adj2 study).mp. | 17 | cardiovascular disease.mp. |
| 19 | or/11-18 | 19 | or/12-18 | 18 | cvd.mp. |
|  |  |  |  | 19 | (coronary adj2 disease).mp. |
| 20 | cardiovascular disease.mp. | 20 | cardiovascular disease.mp. | 20 | exp coronary disease/ |
| 21 | cvd.mp. | 21 | cvd.mp. | 21 | cerebrovascular.mp. |
| 22 | (coronary adj2 disease).mp. | 22 | (coronary adj2 disease).mp. | 22 | cerebral vascular.mp. |
| 23 | exp coronary disease/ | 23 | exp coronary disease/ | 23 | exp brain ischemia/ |
| 24 | cerebrovascular.mp. | 24 | cerebrovascular.mp. | 24 | exp stroke/ |
| 25 | cerebral vascular.mp. | 25 | cerebral vascular.mp. | 25 | exp cerebrovascular disorders/ |
| 26 | exp brain ischemia/ | 26 | exp brain ischemia/ | 26 | exp intracranial arterial diseases/ |
| 27 | exp stroke/ | 27 | exp stroke/ | 27 | exp myocardial infarction/ |
| 28 | exp cerebrovascular disorders/ | 28 | exp cerebrovascular disorders/ | 28 | myocardial infarction.mp. |
| 29 | exp intracranial arterial diseases/ | 29 | exp intracranial arterial diseases/ | 29 | exp myocardial ischemia/ |
| 30 | exp myocardial infarction/ | 30 | exp myocardial infarction/ | 30 | myocardial ischemia.mp. |
| 31 | myocardial infarction.mp. | 31 | myocardial infarction.mp. | 31 | or/17-30 |
| 32 | exp myocardial ischemia/ | 32 | exp myocardial ischemia/ |  |  |
| 33 | myocardial ischemia.mp. | 33 | myocardial ischemia.mp. | 32 | and 7, 16, 31 |
| 34 | or/51-64 | 34 | or/20-34 |  |  |
|  |  |  |  |  |  |
| 35 | and 10, 19, 34 | 35 | and 11, 19, 34 |  |  |

**Supplementary Table 1**. Search Strategy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort** | **AHS-1 & AMS** | **Health Food Shoppers** | **Oxford Vegetarian Study** | **Heidelberg Study** | **EPIC-Oxford** | **AHS-2** | **EPIC-Oxford** |
| **Author** | **Key et al., 1998** | **Appleby et al., 2002** | **Appleby et al., 2002** | **Chang-Claude et al., 2005** | **Key et al., 2009** | **Orlich et al., 2013** | **Crowe et al., 2013** |
| **Pre-specified primary confounding variables** |  |  |  |  |  |  |  |
| Age | x | x | x | x | x | x | x |
| **Pre-specified secondary confounding variables** |  |  |  |  |  |  |  |
| Sex | x | x | x | x | x | x | x |
| Family history of CVD |  |  |  |  |  |  |  |
| Smoking | x | x | x | x | x | x | x |
| Markers of overweight/obesity (BMI, weight, WC, waist to hip ratio) |  |  |  |  |  | x | x |
| Diabetes |  |  | x |  |  |  |  |
| Hypertension |  |  |  |  |  |  |  |
| Dyslipidemia |  |  |  |  |  |  |  |
| Energy intake |  |  |  |  |  | x |  |
| Physical activity |  |  |  | x |  | x | x |
| **Other confounding variables** |  |  |  |  |  |  |  |
| Method of recruitment |  |  |  |  | x |  | x |
| Region |  |  |  |  |  | x | x |
| Education |  |  |  | x |  | x | x |
| SES |  |  |  |  |  |  | x |
| Oral contraceptive use |  |  |  |  |  |  | x |
| HRT use |  |  |  |  |  | x | x |
| Alcohol |  |  |  | x | x | x |  |
| Income |  |  |  |  |  | x |  |
| Marital status |  |  |  |  |  | x |  |
| Sleep |  |  |  |  |  | x |  |
| Menopausal status |  |  |  |  |  | x |  |
| Race/ethnicity |  |  |  |  |  | x |  |
| CVD |  |  | x |  |  |  |  |
| Cancer |  |  | x |  |  |  |  |

Supplementary Table 2. Analysis of confounding variables among included prospective cohort studies. AHS-1=Adventist Health Study-1; AHS-2=Adventist Health Study-2; AMS=Adventist Mortality Study; EPIC=European Prospective Cohort into Cancer and Nutrition.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Selection (max 4)** | | | | **Outcome (max 3)** | | | **Comparability (max 2)** | | **Total** |
| **Representativeness of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at start of study** | **Assessment of outcome** | **Was follow-up long enough for outcomes to occur** | **Adequacy of follow-up of cohort** | **Study controls for primary confounding variable** | **Study controls for secondary confounding variables** |
| Key et al., 1998 (AMS) | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| Key et al., 1998 (AHS-1) | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| Appleby et al., 2002 (OVS) | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 5 |
| Appleby et al., 2002 (HFS) | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| Chang-Claude et al., 2005 (HBS) | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |
| Key et al., 2009 (EPIC-Oxford) | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 7 |
| Crowe et al., 2013  (EPIC-Oxford) | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 7 |
| Orlich et al., 2013 (AHS-2) | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 6 |

Supplementary Table 3. Newcastle Ottawa Scale (NOS) for assessing the quality of prospective cohort studies

AHS-1=Adventist Health Study-1; AHS-2=Adventist Health Study-2; AMS=Adventist Mortality Study; EPIC=European Prospective Cohort into Cancer and Nutrition; HBS=Heidelberg Study; HFS=Health Food Shoppers; OVS=Oxford Vegetarian Study

|  |  |  |
| --- | --- | --- |
| **Removal of** | **RR [95% CI], P-value** | **Heterogeneity** |
| **CVD Mortality** | | |
| Appleby et al., 2002 (OVS) | 0.91 [0.81, 1.02], P=0.10 | I² = 42%, P=0.14 |
| Appleby et al., 2002 (HFS) | 0.91 [0.80, 1.03], P=0.14 | I² = 43%, P=0.13 |
| Chang-Claude et al., 2005 (HBS) | 0.93 [0.84, 1.04], P=0.23 | I² = 42%, P=0.14 |
| Key et al., 2009 (EPIC-Oxford) | 0.91 [0.81, 1.03], P=0.14 | I² = 46%, P=0.12 |
| Orlich et al., 2013 (AHS-2: M) | 0.97 [0.89, 1.05], P=0.46 | I² = 0%, P=0.87 |
| Orlich et al., 2013 (AHS-2: W) | 0.91 [0.80, 1.02], P=0.12 | I² = 43%, P=0.14 |
| **CHD Mortality** | | |
| Key et al., 1998 (AMS) | 0.79 [0.68, 0.92], P=0.003 | I² = 54%, P=0.04 |
| Key et al., 1998 (AHS-1) | 0.82 [0.74, 0.90], P=<0.0001 | I² = 0%, P=0.57 |
| Appleby et al., 2002 (OVS) | 0.75 [0.67, 0.85], P=<0.0001 | I² = 38%, P=0.14 |
| Appleby et al., 2002 (HFS) | 0.76 [0.66, 0.86], P=<0.0001 | I² = 40%, P=0.12 |
| Chang-Claude et al., 2005 (HBS) | 0.78 [0.69, 0.89], P=0.0003 | I² = 54%, P=0.04 |
| Key et al., 2009 (EPIC-Oxford) | 0.77 [0.68, 0.89], P=0.0002 | I² = 53%, P=0.05 |
| Orlich et al., 2013 (AHS-2: M) | 0.79 [0.69, 0.90], P=0.0007 | I² = 53%, P=0.04 |
| Orlich et al., 2013 (AHS-2: W) | 0.77 [0.67, 0.88], P=0.0001 | I² = 50%, P=0.06 |
| **Stroke Mortality** | | |
| Key et al., 1998 (AMS) | 0.99 [0.86, 1.15], P=0.93 | I² = 0%, P=0.83 |
| Key et al.,1998 (AHS-1) | 0.92 [0.72, 1.18], P=0.51 | I² = 58%, P=0.07 |
| Appleby et al., 2002 (HFS) | 0.91 [0.72, 1.15], P=0.43 | I² = 56%, P=0.08 |
| Appleby et al., 2002 (OVS) | 0.89 [0.73, 1.09], P=0.27 | I² = 52%, P=0.10 |
| Key et al., 2009 (EPIC-Oxford) | 0.89 [0.73, 1.09], P=0.26 | I² = 50%, P=0.11 |

**Supplementary Table 4**. Sensitivity analyses: Systematic removal of each study.

AHS-1=Adventist Health Study-1; AHS-2=Adventist Health Study-2; AMS=Adventist Mortality Study; CVD=cardiovascular disease; CHD=coronary heart disease; EPIC=European Prospective Cohort into Cancer and Nutrition; HBS=Heidelberg Study; HFS=Health Food Shoppers; M=men; OVS=Oxford Vegetarian Study; RR=relative risk; W=women

| **Certainty assessment** | | | | | | | | **Relative risk (95% CI)** | **Certainty** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **No. cohort comparisons** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other**  **considerations** |
| **CVD mortality** | 6 | observational studies | not serious | not serious | seriousa | seriousb | none | **RR 0.92** (0.84, 1.02) | ⨁◯◯◯ VERY LOW |
| **CHD mortality** | 8 | observational studies | not serious | not serious | seriousc | not serious | none | **RR 0.78** (0.69, 0.88) | ⨁◯◯◯ VERY LOW |
| **Stroke mortality** | 5 | observational studies | not serious | not serious | seriousd | seriouse | none | **RR 0.92** (0.77, 1.10) | ⨁◯◯◯ VERY LOW |
| **CHD incidence** | 1 | observational studies | not serious | N/Af | seriousg | not serious | none | **RR 0.72** (0.61, 0.85) | ⨁◯◯◯ VERY LOW |

Supplementary Table 5. GRADE assessment for CVD outcomes

a. Serious indirectness for CVD mortality since studies comprising >50% weight in the pooled analysis (85.2%) were conducted in participants who were not representative of the general population. [Participants were either (1) part of the Vegetarian Society of the UK and the news media, with non-vegetarians recruited by the vegetarian participants from among their friends and relatives (OVS cohort); (2) customers of health food shops, members of vegetarian societies and readers of relevant magazines (HFS cohort); (3) individuals following a vegetarian or ‘‘healthy’’ lifestyle who were initially recruited from readers of relevant vegetarian magazines (HBS cohort); (4) Seventh-day Adventists (AHS-2 cohort).] In addition, there were no studies exclusive to or that included subgroup analyses in the diabetes population.

b. Serious imprecision for CVD mortality, as the 95% CIs (0.84, 1.02) overlap with the minimally important difference for clinical benefit (RR=0.95).

c. Serious indirectness for CHD mortality since studies comprising >50% weight in the pooled analysis (91.1%) were conducted in participants who were not representative of the general population. [Participants were either (1) part of the Vegetarian Society of the UK and the news media, with non-vegetarians recruited by the vegetarian participants from among their friends and relatives (OVS cohort); (2) customers of health food shops, members of vegetarian societies and readers of relevant magazines (HFS cohort); (3) individuals following a vegetarian or ‘‘healthy’’ lifestyle who were initially recruited from readers of relevant vegetarian magazines (HBS cohort); (4) Seventh-day Adventists (AMS, AHS-1, AHS-2 cohorts).] In addition, there were no studies exclusive to or that included subgroup analyses in the diabetes population.

d. Serious indirectness for stroke mortality since studies comprising >50% weight in the pooled analysis (83.8%) were conducted in participants who were not representative of the general population. [Participants were either (1) part of the Vegetarian Society of the UK and the news media, with non-vegetarians recruited by the vegetarian participants from among their friends and relatives (OVS cohort); (2) customers of health food shops, members of vegetarian societies and readers of relevant magazines (HFS cohort); (3) Seventh-day Adventists (AMS, AHS-1 cohorts).] In addition, there were no studies exclusive to or that included subgroup analyses in the diabetes population.

e. Serious imprecision for stroke mortality, as the 95% CIs (0.77, 1.10) overlap with the minimally important difference for clinical benefit (RR=0.95) and harm (RR=1.05).

f. Not able to assess inconsistency for CHD incidence as there was only one study available for inclusion.

g. Serious indirectness for CHD incidence as only one cohort available (EPIC-Oxford from the UK). In addition, there were no studies exclusive to or that included subgroup analyses in the diabetes population.

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