Supplementary Material

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|---------------------------|-------|---------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Belch et al., 2008 (POPADAD) | 48 | 640 | 39 | 636 | 2.2% | 1.22 [0.81, 1.84] | |
| Catalano et al., 2007 (CLIPS) | 6 | 185 | 5 | 181 | 0.3% | 1.17 [0.36, 3.78] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 22 | 2231 | 18 | 2264 | 1.0% | 1.24 [0.67, 2.31] | |
| Cook et al., 2007 (WACS) | 137 | 4083 | 161 | 4088 | 7.3% | 0.85 [0.68, 1.07] | |
| GISSI-Prevenzione Investigators, 1999 (GISSI) | 83 | 5660 | 95 | 5664 | 4.3% | 0.87 [0.65, 1.17] | |
| Heart Protection Study CG, 2002 (HPS) | 511 | 10269 | 518 | 10267 | 25.8% | 0.99 [0.88, 1.11] | - |
| Hodis et al., 2002 (VEAPS) | 0 | 177 | 2 | 176 | 0.0% | 0.20 [0.01, 4.11] | • |
| Lee et al., 2005 (WHS) | 241 | 19937 | 246 | 19939 | 11.7% | 0.98 [0.82, 1.17] | |
| Leppala et al., 2000 (ATBC) | 509 | 14238 | 548 | 14281 | 26.1% | 0.93 [0.83, 1.05] | |
| Sesso et al., 2008 (PHS II) | 237 | 7315 | 227 | 7326 | 11.4% | 1.05 [0.87, 1.25] | |
| Steiner et al., 1995 | 3 | 52 | 6 | 48 | 0.2% | 0.46 [0.12, 1.74] | · |
| Yusuf et al., 2000 (HOPE) | 209 | 4761 | 180 | 4780 | 9.6% | 1.17 [0.96, 1.42] | + |
| Total (95% CI) | | 69548 | | 69650 | 100.0% | 0.98 [0.92, 1.04] | • |
| Total events | 2006 | | 2045 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 10.41, df = 11 (P | = 0.49); ² = | 0% | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | 0.2 0.5 1 2 5 Vit E reduces stroke Vit E increases stroke |

Figure S1. Forest plot for the relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population.

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|--|-------|---------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 1.2.1 Subgroup primary prevention | | | | | | | |
| Belch et al., 2008 (POPADAD) | 48 | 640 | 39 | 636 | 2.2% | 1.22 [0.81, 1.84] | |
| Catalano et al., 2007 (CLIPS) | 6 | 185 | 5 | 181 | 0.3% | 1.17 [0.36, 3.78] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 22 | 2231 | 18 | 2264 | 1.0% | 1.24 [0.67, 2.31] | |
| GISSI-Prevenzione Investigators, 1999 (GISSI) | 83 | 5660 | 95 | 5664 | 4.3% | 0.87 [0.65, 1.17] | |
| Hodis et al., 2002 (VEAPS) | 0 | 177 | 2 | 176 | 0.0% | 0.20 [0.01, 4.11] | • |
| Lee et al., 2005 (WHS) | 241 | 19937 | 246 | 19939 | 11.7% | 0.98 [0.82, 1.17] | |
| Leppala et al., 2000 (ATBC) | 509 | 14238 | 548 | 14281 | 26.1% | 0.93 [0.83, 1.05] | |
| Subtotal (95% CI) | | 43068 | | 43141 | 45.6% | 0.96 [0.87, 1.05] | |
| Total events | 909 | | 953 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.84, df = 6 (P = | 0.70 ; $l^2 = 0$? | % | | | | | |
| Test for overall effect: Z = 0.98 (P = 0.33) | | | | | | | |
| 1.2.2 Subgroup secondary prevention | | | | | | | |
| Cook et al., 2007 (WACS) | 137 | 4083 | 161 | 4088 | 7.3% | 0.85 [0.68, 1.07] | |
| Heart Protection Study CG, 2002 (HPS) | 511 | 10269 | 518 | 10267 | 25.8% | 0.99 [0.88, 1.11] | - |
| Sesso et al., 2008 (PHS II) | 237 | 7315 | 227 | 7326 | 11.4% | 1.05 [0.87, 1.25] | |
| Steiner et al., 1995 | 3 | 52 | 6 | 48 | 0.2% | 0.46 [0.12, 1.74] | · |
| Yusuf et al., 2000 (HOPE) | 209 | 4761 | 180 | 4780 | 9.6% | 1.17 [0.96, 1.42] | + |
| Subtotal (95% CI) | | 26480 | | 26509 | 54.4% | 1.00 [0.90, 1.12] | ◆ |
| Total events | 1097 | | 1092 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 5.91, df = 4 (P = | 0.21); I ² = 32 | 2% | | | | | |
| Test for overall effect: Z = 0.08 (P = 0.93) | | | | | | | |
| Total (95% CI) | | 69548 | | 69650 | 100.0% | 0.98 [0.92, 1.04] | • |
| Total events | 2006 | | 2045 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 10.41, df = 11 (F | $P = 0.49$; $ ^2 =$ | 0% | | | | | 0.2 0.5 1 2 5 |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | U.2 U.5 1 2 5 Vit E reduces stroke Vit E increases stroke |
| Test for subgroup differences: Chi ² = 0.47, df = 1 (l | ^o = 0.49), ² = | :0% | | | | | VILE reduces shoke VILE Increases shoke |

Figure S2. Forest plot for the relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population (Type of prevention subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|----------------------------|-------|---------|-------|---------------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 1.3.1 Subgroup synthetic vitamin E | | | | | | | |
| Catalano et al., 2007 (CLIPS) | 6 | 185 | 5 | 181 | 0.3% | 1.17 [0.36, 3.78] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 22 | 2231 | 18 | 2264 | 1.0% | 1.24 [0.67, 2.31] | |
| GISSI-Prevenzione Investigators, 1999 (GISSI) | 83 | 5660 | 95 | 5664 | 4.4% | 0.87 [0.65, 1.17] | |
| Heart Protection Study CG, 2002 (HPS) | 511 | 10269 | 518 | 10267 | 26.5% | 0.99 [0.88, 1.11] | |
| Hodis et al., 2002 (VEAPS) | 0 | 177 | 2 | 176 | 0.0% | 0.20 [0.01, 4.11] | • |
| Leppala et al., 2000 (ATBC) | 509 | 14238 | 548 | 14281 | 26.8% | 0.93 [0.83, 1.05] | |
| Sesso et al., 2008 (PHS II) | 237 | 7315 | 227 | 7326 | 11.7% | 1.05 [0.87, 1.25] | _ _ |
| Subtotal (95% CI) | | 40075 | | 40159 | 70.6 % | 0.97 [0.90, 1.04] | • |
| Total events | 1368 | | 1413 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 3.44, df = 6 (P = | 0.75); I ² = 09 | 6 | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | | |
| 1.3.2 Subgroup natural vitamin E | | | | | | | |
| Cook et al., 2007 (WACS) | 137 | 4083 | 161 | 4088 | 7.5% | 0.85 [0.68, 1.07] | |
| Lee et al., 2005 (WHS) | 241 | 19937 | 246 | 19939 | 12.0% | 0.98 [0.82, 1.17] | -+- |
| Yusuf et al., 2000 (HOPE) | 209 | 4761 | 180 | 4780 | 9.8% | 1.17 [0.96, 1.42] | + |
| Subtotal (95% CI) | | 28781 | | 28807 | 29.4% | 1.00 [0.84, 1.18] | • |
| Total events | 587 | | 587 | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 4.39, df = 2 (P = | 0.11); P= 54 | 96 | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | | |
| Total (95% CI) | | 68856 | | 68966 | 100.0% | 0.98 [0.92, 1.04] | • |
| Total events | 1955 | | 2000 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 8.05, df = 9 (P = | 0.53); I ² = 09 | 6 | | | | | ttttttttt |
| Fest for overall effect: Z = 0.67 (P = 0.51) | | | | | | | |
| Test for subgroup differences: Chi ² = 0.08, df = 1 (F | P = 0.77), P = | 0% | | | | | Vit E reduces stroke Vit E increases stroke |

Figure S3. Forest plot for the relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population (Source of vitamin E subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|----------------------------|-------|---------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 1.4.1 Subgroup high dose | | | | | | | |
| Catalano et al., 2007 (CLIPS) | 6 | 185 | 5 | 181 | 0.3% | 1.17 [0.36, 3.78] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 22 | 2231 | 18 | 2264 | 1.0% | 1.24 [0.67, 2.31] | |
| Cook et al., 2007 (WACS) | 137 | 4083 | 161 | 4088 | 7.3% | 0.85 [0.68, 1.07] | |
| GISSI-Prevenzione Investigators, 1999 (GISSI) | 83 | 5660 | 95 | 5664 | 4.3% | 0.87 [0.65, 1.17] | |
| Heart Protection Study CG, 2002 (HPS) | 511 | 10269 | 518 | 10267 | 25.8% | 0.99 [0.88, 1.11] | |
| Hodis et al., 2002 (VEAPS) | 0 | 177 | 2 | 176 | 0.0% | 0.20 [0.01, 4.11] | • |
| Lee et al., 2005 (WHS) | 241 | 19937 | 246 | 19939 | 11.7% | 0.98 [0.82, 1.17] | |
| Steiner et al., 1995 | 3 | 52 | 6 | 48 | 0.2% | 0.46 [0.12, 1.74] | · |
| Yusufetal., 2000 (HOPE) | 209 | 4761 | 180 | 4780 | 9.6% | 1.17 [0.96, 1.42] | _ - |
| Subtotal (95% CI) | | 47355 | | 47407 | 60.3% | 0.99 [0.91, 1.07] | • |
| Total events | 1212 | | 1231 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 8.06, df = 8 (P = 0 | 0.43); I ² = 19 | 6 | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.72) | | | | | | | |
| 1.4.2 Subgroup low dose | | | | | | | |
| Belch et al., 2008 (POPADAD) | 48 | 640 | 39 | 636 | 2.2% | 1.22 [0.81, 1.84] | |
| Leppala et al., 2000 (ATBC) | 509 | 14238 | 548 | 14281 | 26.1% | 0.93 [0.83, 1.05] | |
| Sesso et al., 2008 (PHS II) | 237 | 7315 | 227 | 7326 | 11.4% | 1.05 [0.87, 1.25] | _ |
| Subtotal (95% CI) | | 22193 | | 22243 | 39.7% | 0.99 [0.88, 1.10] | • |
| Total events | 794 | | 814 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.34, df = 2 (P = 0 | 0.31); I ² = 14 | % | | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | | | | |
| Total (95% CI) | | 69548 | | 69650 | 100.0% | 0.98 [0.92, 1.04] | • |
| Total events | 2006 | | 2045 | | | - / * |] |
| Heterogeneity: Tau ² = 0.00; Chi ² = 10.41, df = 11 (P | | 0% | | | | | t <u> t</u> t t t |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | 0.2 0.5 1 2 5 Vit E reduces stroke Vit E increases stroke |
| Test for subgroup differences; Chi ² = 0.00, df = 1 (P | = 1.00), l ² = | 0% | | | | | VILE reduces stroke VILE Increases stroke |
| | | | | | | | |

Figure S4. Forest plot for the relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population (Dosage of vitamin E subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|---------------------------|-------|---------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| GISSI-Prevenzione Investigators, 1999 (GISSI) | 39 | 2830 | 41 | 2828 | 9.5% | 0.95 [0.62, 1.47] | |
| Hodis et al., 2002 (VEAPS) | 0 | 177 | 2 | 176 | 0.2% | 0.20 [0.01, 4.11] 🔸 | |
| Leppala et al., 2000 (ATBC) | 251 | 7120 | 252 | 7153 | 60.8% | 1.00 [0.84, 1.19] | |
| Sesso et al., 2008 (PHS II) | 133 | 3659 | 113 | 3653 | 29.5% | 1.18 [0.92, 1.50] | + |
| Total (95% CI) | | 13786 | | 13810 | 100.0% | 1.04 [0.91, 1.19] | ◆ |
| Total events | 423 | | 408 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.45, df = 3 (F | = 0.49); I ² = | 0% | | | | - | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | | Vit E reduces stroke Vit E increases stroke |

Figure S5. Forest plot for the relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population (Vitamin E alone).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|---------------------------|-------|---------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Belch et al., 2008 (POPADAD) | 12 | 640 | 5 | 636 | 3.9% | 2.38 [0.85, 6.73] | |
| Catalano et al., 2007 (CLIPS) | 3 | 185 | 0 | 181 | 0.5% | 6.85 [0.36, 131.67] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 2 | 2231 | 5 | 2264 | 1.7% | 0.41 [0.08, 2.09] | |
| Cook et al., 2007 (WACS) | 18 | 4083 | 15 | 4088 | 7.8% | 1.20 [0.61, 2.38] | |
| Heart Protection Study CG, 2002 (HPS) | 108 | 10269 | 107 | 10267 | 22.6% | 1.01 [0.77, 1.32] | -+- |
| Lamas et al., 2013 (TACT) | 8 | 853 | 15 | 855 | 5.5% | 0.53 [0.23, 1.25] | |
| Lee et al., 2005 (WHS) | 21 | 19937 | 24 | 19939 | 9.8% | 0.88 [0.49, 1.57] | |
| Leppala et al., 2000 (ATBC) | 90 | 14238 | 70 | 14281 | 20.1% | 1.29 [0.94, 1.76] | |
| Li et al., 1993 (Linxian) | 22 | 1657 | 35 | 1661 | 11.3% | 0.63 [0.37, 1.07] | |
| Sesso et al., 2008 (PHS II) | 45 | 7315 | 56 | 7326 | 16.2% | 0.80 [0.54, 1.19] | |
| Stephens et al., 1996 (CHAOS) | 1 | 1035 | 1 | 967 | 0.6% | 0.93 [0.06, 14.92] | · · · · · · · · · · · · · · · · · · · |
| Total (95% CI) | | 62443 | | 62465 | 100.0% | 0.96 [0.77, 1.20] | • |
| Total events | 330 | | 333 | | | | |
| Heterogeneity: Tau ² = 0.04; Chi ² = 14.70, df = 10 (P | = 0.14); l ² = | 32% | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.73) | | | | | | | Vit E reduces stroke Vit E increases stroke |
| | | | | | | | VILL reduces subke VILL increases subke |

Figure S6. Forest plot for the relative risks of the effect of vitamin E on fatal stroke for individual trials and for the pooled population.

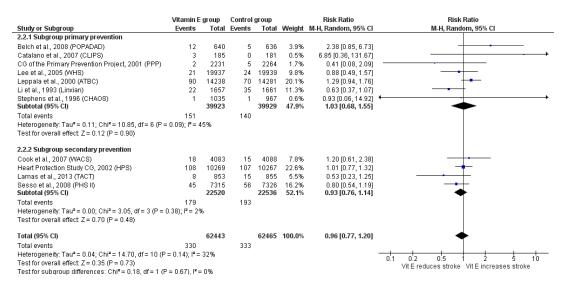


Figure S7. Forest plot for the relative risks of the effect of vitamin E on fatal stroke for individual trials and for the pooled population (Type of prevention subgroup).

| | Vitamin E | | Control | | | Risk Ratio | Risk Ratio |
|--|----------------------------------|-------|---------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 2.3.1 Subgroup synthetic vitamin E | | | | | | | |
| Catalano et al., 2007 (CLIPS) | 3 | 185 | 0 | 181 | 0.5% | 6.85 [0.36, 131.67] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 2 | 2231 | 5 | 2264 | 1.5% | 0.41 [0.08, 2.09] | |
| Heart Protection Study CG, 2002 (HPS) | 108 | 10269 | 107 | 10267 | 25.7% | 1.01 [0.77, 1.32] | |
| Leppala et al., 2000 (ATBC) | 90 | 14238 | 70 | 14281 | 22.0% | 1.29 [0.94, 1.76] | + - - |
| Li et al., 1993 (Linxian) | 22 | 1657 | 35 | 1661 | 11.1% | 0.63 [0.37, 1.07] | |
| Sesso et al., 2008 (PHS II) | 45 | 7315 | 56 | 7326 | 16.9% | 0.80 [0.54, 1.19] | |
| Subtotal (95% CI) | | 35895 | | 35980 | 77.7% | 0.94 [0.72, 1.24] | • |
| Total events | 270 | | 273 | | | | |
| Heterogeneity: Tau ² = 0.05; Chi ² = 9.45, df = 5 (P = 1 | 0.09); I ² = 47 | '% | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | | | |
| 2.3.2 Subgroup natural vitamin E | | | | | | | |
| Cook et al., 2007 (WACS) | 18 | 4083 | 15 | 4088 | 7.3% | 1.20 [0.61, 2.38] | |
| Lamas et al., 2013 (TACT) | 8 | 853 | 15 | 855 | 5.0% | 0.53 [0.23, 1.25] | |
| Lee et al., 2005 (WHS) | 21 | 19937 | 24 | 19939 | 9.5% | 0.88 [0.49, 1.57] | + |
| Stephens et al., 1996 (CHAOS) | 1 | 1035 | 1 | 967 | 0.5% | 0.93 [0.06, 14.92] | |
| Subtotal (95% CI) | | 25908 | | 25849 | 22.3% | 0.88 [0.59, 1.29] | |
| Total events | 48 | | 55 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 2.11, df = 3 (P = I | 0.55); I ² = 09 | 6 | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | | |
| Total (95% CI) | | 61803 | | 61829 | 100.0% | 0.94 [0.77, 1.15] | • |
| Total events | 318 | | 328 | | | | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 11.86, df = 9 (P = | 0.22); I ² = 2 | 24% | | | | | |
| Test for overall effect: Z = 0.63 (P = 0.53) | | | | | | | 0.1 0.2 0.5 1 2 5 10 VitEreduces stroke VitEincreases stroke |
| Test for subgroup differences: Chi ² = 0.09, df = 1 (P | = 0.77), l ² = | :0% | | | | | VILE reduces stroke VILE Increases stroke |
| | | | | | | | |

Figure S8. Forest plot for the relative risks of the effect of vitamin E on fatal stroke for individual trials and for the pooled population (Source of vitamin E subgroup).

| | Vitamin E | | Control | | | Risk Ratio | Risk Ratio |
|--|--|--|--|--|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 2.4.1 Subgroup high dose | | | | | | | |
| Catalano et al., 2007 (CLIPS) | 3 | 185 | 0 | 181 | 0.5% | 6.85 [0.36, 131.67] | |
| CG of the Primary Prevention Project, 2001 (PPP) | 2 | 2231 | 5 | 2264 | 1.7% | 0.41 [0.08, 2.09] | |
| Cook et al., 2007 (WACS) | 18 | 4083 | 15 | 4088 | 7.8% | 1.20 [0.61, 2.38] | |
| Heart Protection Study CG, 2002 (HPS) | 108 | 10269 | 107 | 10267 | 22.6% | 1.01 [0.77, 1.32] | |
| Lamas et al., 2013 (TACT) | 8 | 853 | 15 | 855 | 5.5% | 0.53 [0.23, 1.25] | |
| Lee et al., 2005 (WHS) | 21 | 19937 | 24 | 19939 | 9.8% | 0.88 [0.49, 1.57] | |
| | 1 | | 1 | | | | · · · · · · · · · · · · · · · · · · · |
| | | 38593 | | 38561 | 48.5% | 0.96 [0.77, 1.19] | • |
| | | | 167 | | | | |
| | 0.52); I² = 09 | Ко | | | | | |
| Test for overall effect: Z = 0.36 (P = 0.72) | | | | | | | |
| 2.4.2 Subgroup low dose | | | | | | | |
| Belch et al., 2008 (POPADAD) | 12 | 640 | 5 | 636 | 3.9% | 2.38 [0.85, 6.73] | |
| Leppala et al., 2000 (ATBC) | 90 | 14238 | 70 | 14281 | 20.1% | 1.29 [0.94, 1.76] | + |
| Li et al., 1993 (Linxian) | 22 | 1657 | 35 | 1661 | 11.3% | 0.63 [0.37, 1.07] | |
| Sesso et al., 2008 (PHS II) | 45 | 7315 | 56 | 7326 | 16.2% | 0.80 [0.54, 1.19] | |
| Subtotal (95% CI) | | 23850 | | 23904 | 51.5% | 1.01 [0.66, 1.55] | • |
| Total events | 169 | | 166 | | | | |
| Heterogeneity: Tau ² = 0.12; Chi ² = 9.35, df = 3 (P = 0 | 0.02); I ² = 68 | 3% | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | | |
| Total (95% CI) | | 62443 | | 62465 | 100.0% | 0.96 [0.77, 1.20] | |
| Total events | 330 | | 333 | | | | |
| Heterogeneity: Tau ² = 0.04; Chi ² = 14.70, df = 10 (P | = 0.14); 2= | 32% | | | | | |
| Test for overall effect; Z = 0.35 (P = 0.73) | | - | | | | | |
| Test for subgroup differences: Chi ² = 0.04, df = 1 (P | = 0.84), l ² = | :0% | | | | | VILE reduces stroke VILE Increases stroke |
| Lee et al., 2005 (WHS) Stephens et al., 1996 (CHAOS) Subtotal (55% CI) Total events Heterogeneily: Tau ² = 0.00; Chi ² = 5.21, df = 6 (P = (Test for overall effect Z = 0.36 (P = 0.72) 2.4.2 Subgroup low dose Beich et al., 2008 (POPADAD) Leppala et al., 2008 (POPADAD) Leppala et al., 2008 (PHB II) Subtotal (95% CI) Total events Heterogeneily: Tau ² = 0.12; Chi ² = 9.35, df = 3 (P = (Test for overall effect Z = 0.04 (P = 0.97) Total events Heterogeneily: Tau ² = 0.04; Chi ² = 14.70, df = 10 (P Test for overall effect Z = 0.35 (P = 0.73) | 21 161 1.52); = 0' 12 20 22 45 169 0.02); = 6(330 = 0.14); = | 19937 1035 38593 % 640 14238 1657 7315 23850 3% 62443 32% | 24 1 167 5 70 35 56 166 | 19939 967 38561 636 14281 1661 7326 23904 | 9.8% 0.6% 48.5% 20.1% 11.3% 16.2% 51.5% | 0.88 [0.49, 1.57] 0.93 [0.06, 14.92] 0.96 [0.77, 1.19] 2.38 [0.85, 6.73] 1.29 [0.94, 1.76] 0.63 [0.37, 1.07] 0.80 [0.54, 1.19] 1.01 [0.66, 1.55] | 0.1 0.2 0.5 12 5 10 Vit E reduces stroke |

Figure S9. Forest plot for the relative risks of the effect of vitamin E on fatal stroke for individual trials and for the pooled population (Dosage of vitamin E subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|---|---------------------------|-------|---------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Belch et al., 2008 (POPADAD) | 36 | 640 | 34 | 636 | 3.5% | 1.05 [0.67, 1.66] | |
| Catalano et al., 2007 (CLIPS) | 3 | 185 | 5 | 181 | 0.4% | 0.59 [0.14, 2.42] | · |
| CG of the Primary Prevention Project, 2001 (PPP) | 20 | 2231 | 13 | 2264 | 1.6% | 1.56 [0.78, 3.13] | |
| Cook et al., 2007 (WACS) | 119 | 4083 | 146 | 4088 | 11.2% | 0.82 [0.64, 1.04] | |
| Heart Protection Study CG, 2002 (HPS) | 430 | 10269 | 435 | 10267 | 25.8% | 0.99 [0.87, 1.13] | |
| Lee et al., 2005 (WHS) | 220 | 19937 | 222 | 19939 | 16.4% | 0.99 [0.82, 1.19] | |
| Leppala et al., 2000 (ATBC) | 419 | 14238 | 478 | 14281 | 26.1% | 0.88 [0.77, 1.00] | |
| Milman et al., 2008 (ICARE) | 6 | 726 | 11 | 708 | 0.8% | 0.53 [0.20, 1.43] | |
| Sesso et al., 2008 (PHS II) | 192 | 7315 | 171 | 7326 | 14.3% | 1.12 [0.92, 1.38] | +• |
| Total (95% CI) | | 59624 | | 59690 | 100.0% | 0.96 [0.88, 1.05] | • |
| Total events | 1445 | | 1515 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 10.03, df = 8 (P = | 0.26); I ² = 2 | 20% | | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | | | | Vit E reduces stroke Vit E increases stroke |

Figure S10. Forest plot for the relative risks of the effect of vitamin E on non-fatal stroke for individual trials and for the pooled population.

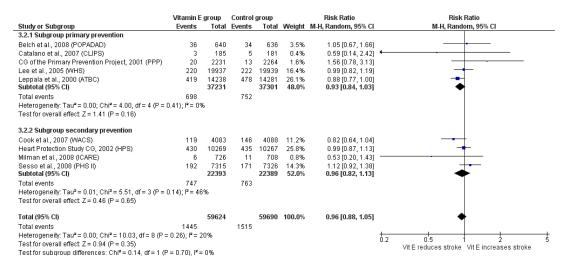


Figure S11. Forest plot for the relative risks of the effect of vitamin E on non-fatal stroke for individual trials and for the pooled population (Type of prevention subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|----------------------------|---------------|---------|---------------|-----------------------|--|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| 3.3.1 Subgroup synthetic vitamin E | | | | | | | |
| Catalano et al., 2007 (CLIPS) | 3 | 185 | 5 | 181 | 0.5% | 0.59 [0.14, 2.42] | · |
| CG of the Primary Prevention Project, 2001 (PPP) | 20 | 2231 | 13 | 2264 | 1.9% | 1.56 [0.78, 3.13] | |
| Heart Protection Study CG, 2002 (HPS) | 430 | 10269 | 435 | 10267 | 25.7% | 0.99 [0.87, 1.13] | -+- |
| Leppala et al., 2000 (ATBC) | 419 | 14238 | 478 | 14281 | 26.0% | 0.88 [0.77, 1.00] | |
| Sesso et al., 2008 (PHS II) Subtotal (95% CI) | 192 | 7315 34238 | 171 | 7326 34319 | 15.4% 69.4% | 1.12 [0.92, 1.38] 0.99 [0.87, 1.12] | ◆ |
| Total events | 1064 | | 1102 | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 6.60, df = 4 (P = Test for overall effect: Z = 0.21 (P = 0.83) | 0.16); I ^z = 3! | 3% | | | | | |
| 3.3.2 Subgroup natural vitamin E | | | | | | | |
| Cook et al., 2007 (WACS) | 119 | 4083 | 146 | 4088 | 12.3% | 0.82 [0.64, 1.04] | |
| Lee et al., 2005 (WHS) | 220 | 19937 | 222 | 19939 | 17.4% | 0.99 [0.82, 1.19] | -+- |
| Milman et al., 2008 (ICARE) Subtotal (95% CI) | 6 | 726 24746 | 11 | 708 24735 | 0.9% 30.6 % | 0.53 [0.20, 1.43] 0.89 [0.74, 1.08] | |
| Total events | 345 | | 379 | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 2.75, df = 2 (P = 1) Test for overall effect: $Z = 1.14$ (P = 0.25) | 0.25); I² = 2) | 7% | | | | | |
| Total (95% CI) | | 58984 | | 59054 | 100.0% | 0.96 [0.87, 1.05] | • |
| Total events | 1409 | | 1481 | | | | |
| Heterogeneity: Tau ² = 0.01; Chi ² = 9.85, df = 7 (P = Test for overall effect: $Z = 0.91$ (P = 0.36) Test for subgroup differences: Chi ² = 0.70, df = 1 (F | | | | | | | 0.2 0.5 1 2 Vit E reduces stroke Vit E increases stroke |

Figure S12. Forest plot for the relative risks of the effect of vitamin E on non-fatal stroke for individual trials and for the pooled population (Source of vitamin E subgroup).

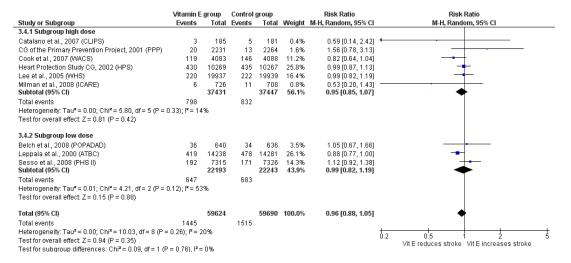


Figure S13. Forest plot for the relative risks of the effect of vitamin E on non-fatal stroke for individual trials and for the pooled population (Dosage of vitamin E subgroup).

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|--------------|-------------|---------|-------|--------|---------------------|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Cook et al., 2007 (WACS) | 15 | 4083 | 10 | 4088 | 4.8% | 1.50 [0.68, 3.34] | |
| Heart Protection Study CG, 2002 (HPS) | 51 | 10269 | 53 | 10267 | 20.6% | 0.96 [0.66, 1.41] | |
| Lee et al., 2005 (WHS) | 44 | 19937 | 48 | 19939 | 18.2% | 0.92 [0.61, 1.38] | |
| Leppala et al., 2000 (ATBC) | 108 | 14238 | 89 | 14281 | 38.8% | 1.22 [0.92, 1.61] | |
| Sesso et al., 2008 (PHS II) | 39 | 7315 | 23 | 7326 | 11.5% | 1.70 [1.02, 2.84] | |
| Steiner et al., 1995 | 2 | 52 | 0 | 48 | 0.3% | 4.62 [0.23, 93.91] | |
| Yusuf et al., 2000 (HOPE) | 17 | 4761 | 13 | 4780 | 5.8% | 1.31 [0.64, 2.70] | |
| Total (95% CI) | | 60655 | | 60729 | 100.0% | 1.17 [0.98, 1.39] | • |
| Total events | 276 | | 236 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 5.74, d | f= 6 (P = 0. | 45); I² = 0 |)% | | | | 0.01 0.1 1 10 100 |
| Test for overall effect: Z = 1.73 (P = 0.08) | | | | | | | Vit E reduces stroke Vit E increases stroke |

Figure S14. Forest plot for the relative risks of the effect of vitamin E on haemorrhagic stroke for individual trials and for the pooled population.

| | Vitamin E | group | Control | group | | Risk Ratio | Risk Ratio |
|--|---------------|---------------------|---------|-------|--------|---------------------|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Boaz et al., 2000 (SPACE) | 5 | 97 | 6 | 99 | 0.5% | 0.85 [0.27, 2.70] | · · · · · · · · · · · · · · · · · · · |
| Cook et al., 2007 (WACS) | 121 | 4083 | 150 | 4088 | 11.0% | 0.81 [0.64, 1.02] | |
| Heart Protection Study CG, 2002 (HPS) | 345 | 10269 | 354 | 10267 | 27.0% | 0.97 [0.84, 1.13] | _ |
| Lee et al., 2005 (WHS) | 194 | 19937 | 197 | 19939 | 15.4% | 0.98 [0.81, 1.20] | |
| Leppala et al., 2000 (ATBC) | 373 | 14238 | 434 | 14281 | 30.4% | 0.86 [0.75, 0.99] | |
| Sesso et al., 2008 (PHS II) | 191 | 7315 | 196 | 7326 | 15.5% | 0.98 [0.80, 1.19] | |
| Steiner et al., 1995 | 1 | 52 | 6 | 48 | 0.1% | 0.15 [0.02, 1.23] | • |
| Total (95% CI) | | 55991 | | 56048 | 100.0% | 0.92 [0.85, 0.99] | • |
| Total events | 1230 | | 1343 | | | | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 6.31, d | f= 6 (P = 0.3 | 39); I ² = 6 | 5% | | | | |
| Test for overall effect: Z = 2.10 (P = 0.04) | | | | | | | 0.5 0.7 1 1.5 2 Vit E reduces stroke Vit E increases stroke |

Figure S15. Forest plot for the relative risks of the effect of vitamin E on ischaemic stroke for individual trials and for the pooled population.

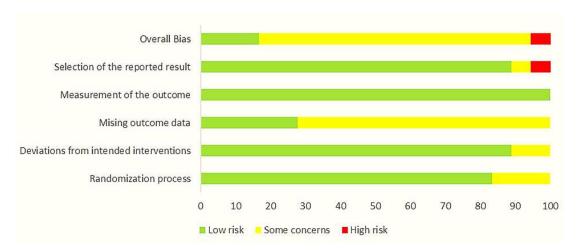


Figure S16. Risk of bias graph shows review authors' judgements about each risk of bias items presented as percentages across all included studies.

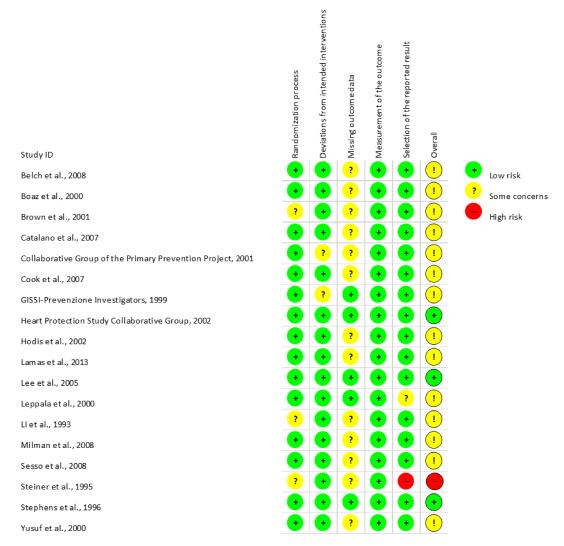


Figure S17. Risk of bias summary shows review authors' judgements about each risk of bias items for each included study.

Table S1. GRADE quality assessment for the study findings was summarised as follows.

| | Certainty assessment | | | | | | | Nº of patients | | Effect | | Importance |
|------------------|----------------------|-----------------|---------------|--------------|-------------|-------------------------|------------|----------------|----------------------|----------------------|-----------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vitamin E | Control | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| The effec | t of vitamin E | on total strok | e | | | | | | | | | |
| 40 | | | | | | | 0000000540 | 0045/00050 | DD 000 | | - | |

| 12 | randomised trials | serious | not serious | not serious | not serious | none | 2006/69548 (2.9%) | 2045/69650 (2.9%) | RR 0.98 (0.92 to 1.04) | 1 fewer per 1,000 (from 2 fewer to 1 more) | | | |
|----|----------------------|---------|-------------|-------------|-------------|------|----------------------|----------------------|-------------------------------|---|--|--|--|
|----|----------------------|---------|-------------|-------------|-------------|------|----------------------|----------------------|-------------------------------|---|--|--|--|

The effect of vitamin E on fatal stroke

| 11 | randomised trials | not serious | not serious | not serious | not serious | none | 330/62443 (0.5%) | 333/62465 (0.5%) | RR 0.96 (0.77 to 1.20) | 0 fewer per 1,000 (from 1 fewer to 1 more) | ⊕⊕⊕⊕ _{HIGH} | |
|----|----------------------|-------------|-------------|-------------|-------------|------|---------------------|---------------------|---------------------------|---|-------------------------|--|
|----|----------------------|-------------|-------------|-------------|-------------|------|---------------------|---------------------|---------------------------|---|-------------------------|--|

The effect of vitamin E on non fatal stroke

| 9 | randomised trials | not serious | not serious | not serious | not serious | none | 1445/59624 (2.4%) | 1515/59690 (2.5%) | RR 0.96 (0.88 to 1.05) | 1 fewer per 1,000 (from 3 fewer to 1 more) | ⊕⊕⊕⊕ _{HIGH} | | |
|---|----------------------|-------------|-------------|-------------|-------------|------|----------------------|----------------------|---------------------------|---|-------------------------|--|--|
|---|----------------------|-------------|-------------|-------------|-------------|------|----------------------|----------------------|---------------------------|---|-------------------------|--|--|

The effect of vitamin E on haemorrhagic stroke

| 7 | randomised trials | serious | not serious | not serious | very serious | none | 276/60655 (0.5%) | 236/60729 (0.4%) | RR 1.17 (0.98 to 1.39) | 1 more per 1,000 (from 0 fewer to 2 more) | | |
|---|----------------------|---------|-------------|-------------|--------------|------|---------------------|---------------------|-------------------------------|--|--|--|
|---|----------------------|---------|-------------|-------------|--------------|------|---------------------|---------------------|-------------------------------|--|--|--|

The effect of vitamin E on ischaemic stroke

| 7 | randomised trials | serious | not serious | not serious | not serious | none | 1230/55991 (2.2%) | 1343/56048 (2.4%) | RR 0.92 (0.85 to 0.99) | 2 fewer per 1,000 (from 4 fewer to 0 fewer) | | |
|---|----------------------|---------|-------------|-------------|-------------|------|----------------------|----------------------|-------------------------------|--|--|--|
|---|----------------------|---------|-------------|-------------|-------------|------|----------------------|----------------------|-------------------------------|--|--|--|

CI: Confidence interval; RR: Risk ratio