

## Supplementary data

**Supplementary Figure 1.** PRISMA search diagram.

**Supplementary Figure 2.** Risk of bias graph.

**Supplementary Figure 3.** Risk of bias summary.

**Supplementary Figure 4.** Subgroup analysis based on aspirin dose showed that different daily doses of aspirin were not associated with significant reductions in total cancer incidence, total cancer mortality, or all-cause mortality. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

**Supplementary Figure 5.** The results of meta-regression analyses showing that the total cancer incidence, cancer mortality and all-cause mortality did not vary significantly with respect to the daily dose of aspirin (from  $\leq 100$  mg to  $> 300$  mg). A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

**Supplementary Figure 6.** Subgroup analysis based on follow-up duration showed that different follow-up durations (1-5 years, 5-10 years, or  $> 10$  years) were not associated with significant reductions in total cancer incidence, cancer mortality and all-cause mortality. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

**Supplementary Figure 7.** The meta-regression analysis showed that total cancer incidence, cancer mortality and all-cause mortality did not vary significantly with respect to follow-up duration (1-5 years to  $> 10$  years). A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

**Supplementary Figure 8.** Subgroup analysis showing that the cancer incidence, cancer mortality and all-cause mortality were not reduced by low-dose aspirin ( $\leq 100$  mg/day) use for more than five years.

**Supplementary Figure 9.** Subgroup analysis based on study populations showing that aspirin use did not decrease the total cancer incidence, total cancer mortality or all-cause mortality in five

different subgroups of participants, including the healthy population, patients with diabetes mellitus, participants with CVD or an increased risk of CVD, individuals with an increased risk of cancer, or patients with peripheral arterial disease or venous thromboembolism. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

**Supplementary Figure 10.** Subgroup analysis based on the daily dose of aspirin showed that all three different daily doses of aspirin ( $\leq 100$  mg, 100-300 mg, or  $> 300$  mg daily) significantly increased the risk of major bleeding and total bleeding events. A) Major bleeding, B) total bleeding events.

**Supplementary Figure 11.** Subgroup analysis based on follow-up duration showed that the risk of major bleeding and total bleeding events significantly increased with different follow-up durations (1-5 years, 5-10 years, or  $> 10$  years). A) Major bleeding, B) total bleeding events.

**Supplementary Figure 12.** Trial sequential analysis indicated that aspirin use was not significantly superior to no aspirin, and the cumulated sample size of all the RCTs reached the required information size (IS) needed for a conclusive and reliable meta-analysis, suggesting that the findings of the meta-analysis were robust for the cancer incidence.

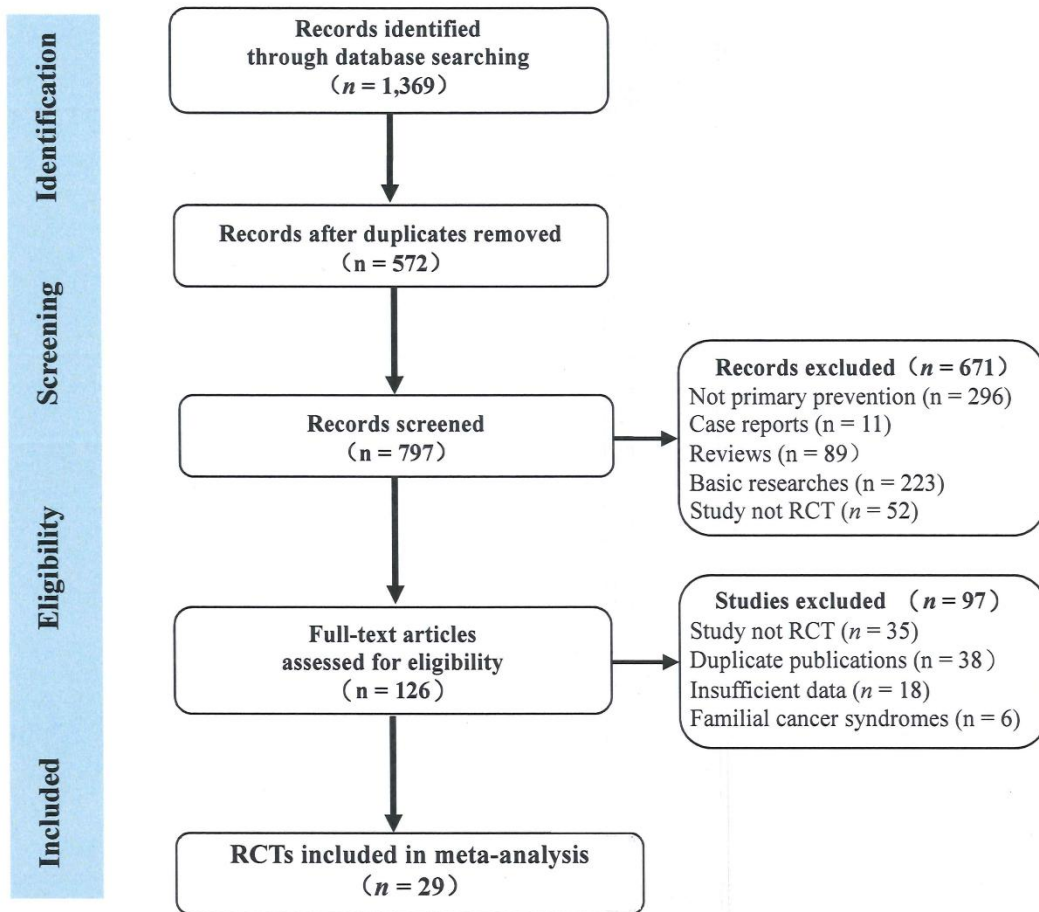
**Supplementary Figure 13.** The funnel plots of total cancer incidence (the primary outcome).

**Supplementary Table 1.** The methodologic quality of the included trials was assessed using the Cochrane risk-of-bias tool.

**Supplementary Table 2.** GRADE evidence profile: long-term aspirin use for cancer primary prevention.

**Supplementary Table 3.** Sensitivity analyses.

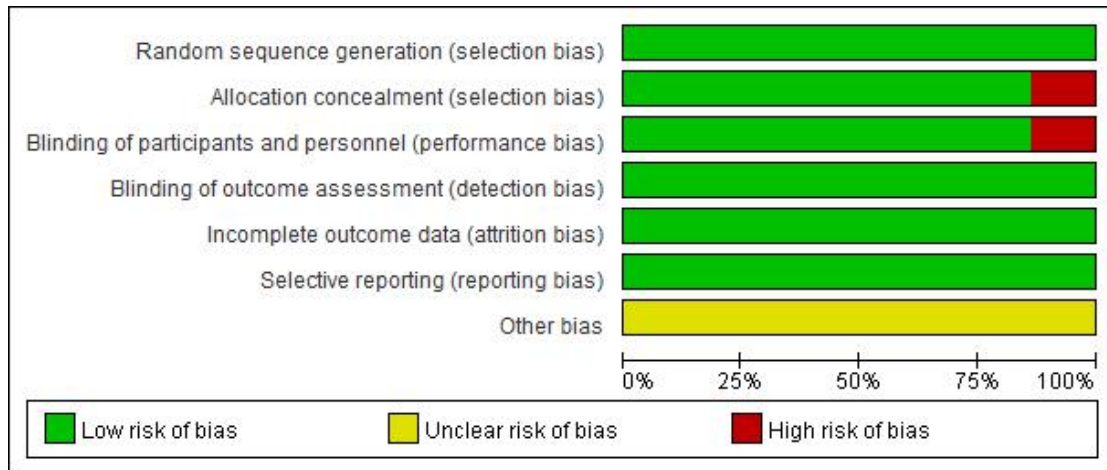
**Supplementary Figure 1: PRISMA diagram of searching**



RCT, randomised controlled trial;

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

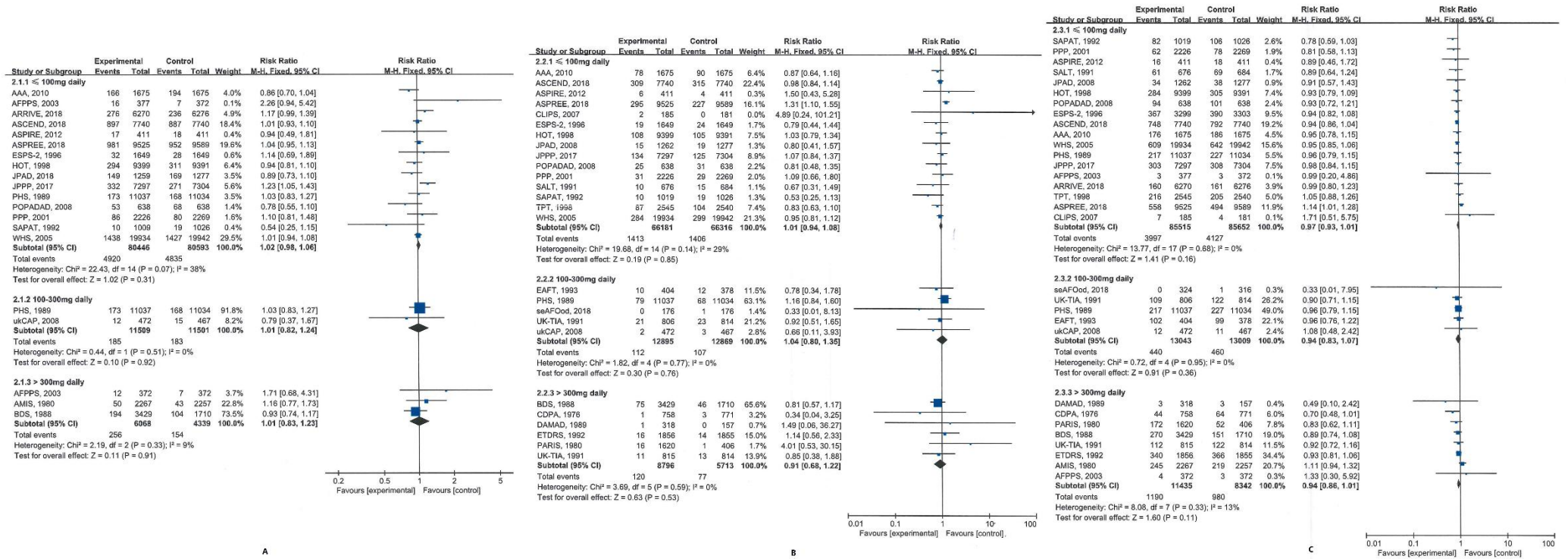
**Supplementary Figure 2: Risk of bias graph.**



**Supplementary Figure 3: Risk of bias summary.**

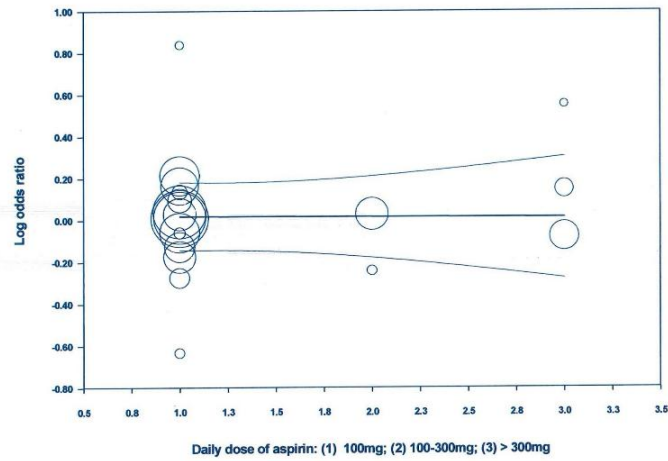
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AAA, 2010	+	+	+	+	+	+	?
AFPPS, 2003	+	+	+	+	+	+	?
AMIS, 1980	+	+	+	+	+	+	?
ARRIVE, 2018	+	+	+	+	+	+	?
ASCEND, 2018	+	+	+	+	+	+	?
ASPIRE, 2012	+	+	+	+	+	+	?
ASPREE, 2018	+	+	+	+	+	+	?
BDS, 1988	+	●	●	+	+	+	?
CDPA, 1976	+	+	+	+	+	+	?
CLIPS, 2007	+	+	+	+	+	+	?
DAMAD, 1989	+	+	+	+	+	+	?
EAFT, 1993	+	+	+	+	+	+	?
ESPS-2, 1996	+	+	+	+	+	+	?
ETDRS, 1992	+	+	+	+	+	+	?
HOT, 1998	+	+	+	+	+	+	?
JPAD, 2008/2017/2018	+	●	●	+	+	+	?
JPPP, 2017	+	●	●	+	+	+	?
PARIS, 1980	+	+	+	+	+	+	?
PHS, 1989/1998	+	+	+	+	+	+	?
POPADAD, 2008	+	+	+	+	+	+	?
PPP, 2001	+	●	●	+	+	+	?
REDUCE, 2015	+	+	+	+	+	+	?
SALT, 1991	+	+	+	+	+	+	?
SAPAT, 1992	+	+	+	+	+	+	?
seAFood, 2018	+	+	+	+	+	+	?
TPT, 1998	+	+	+	+	+	+	?
ukCAP, 2008	+	+	+	+	+	+	?
UK-TIA, 1991	+	+	+	+	+	+	?
WHS, 2005	+	+	+	+	+	+	?

**Supplementary Figure 4.** Subgroup analysis based on aspirin dose showed that different daily doses of aspirin were not associated with significant reductions in total cancer incidence, total cancer mortality, or all-cause mortality. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.



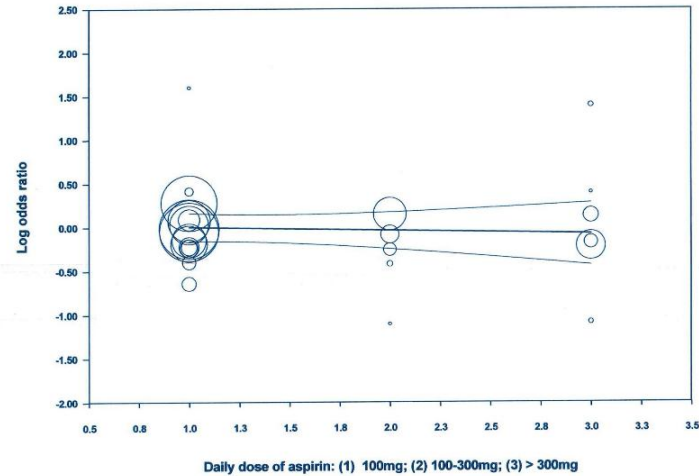
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Regression of Log odds ratio on Daily dose of aspirin: (1) 100mg; (2) 100-300mg; (3)  $> 300$ mg



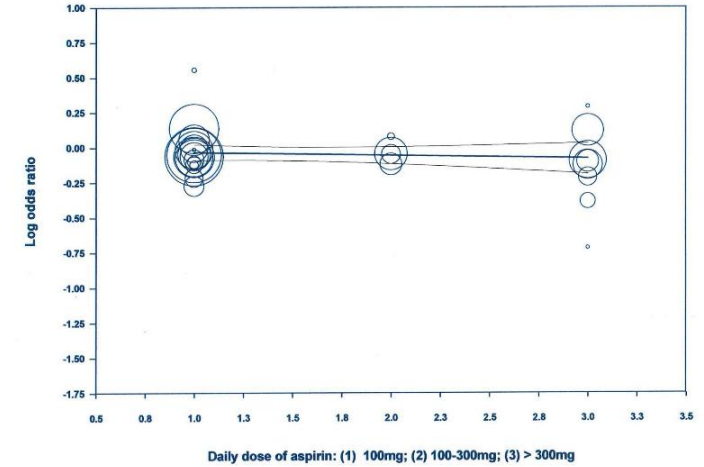
A

Regression of Log odds ratio on Daily dose of aspirin: (1) 100mg; (2) 100-300mg; (3)  $> 300$ mg



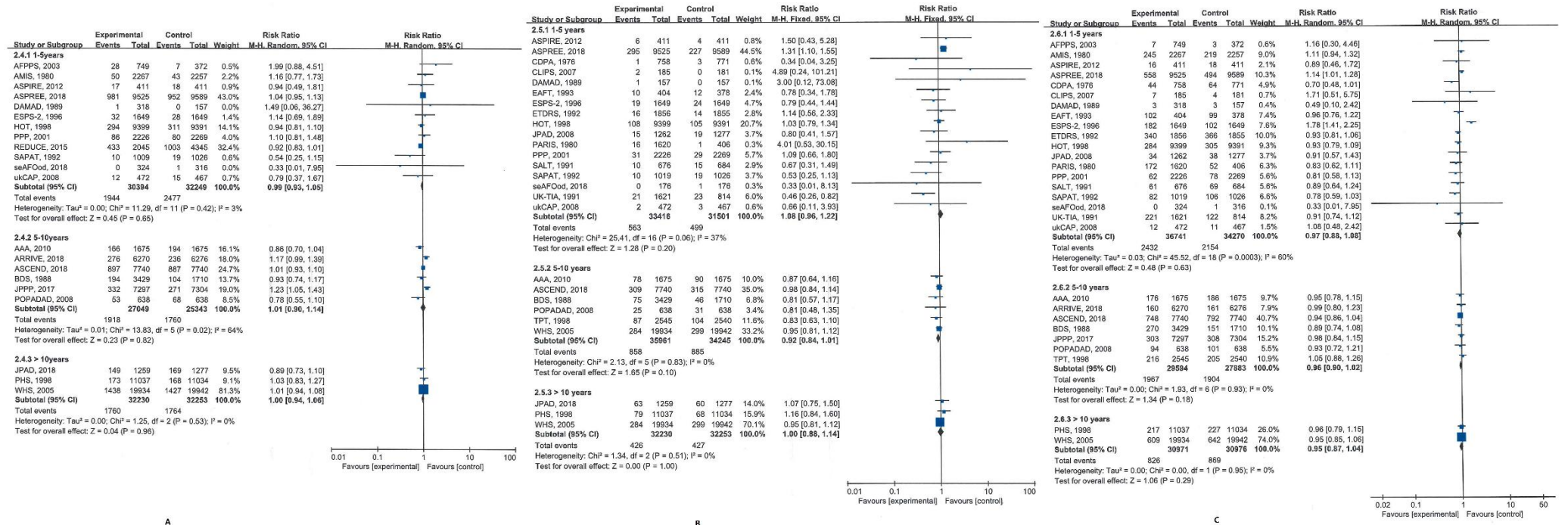
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Regression of Log odds ratio on Daily dose of aspirin: (1) 100mg; (2) 100-300mg; (3)  $> 300$ mg



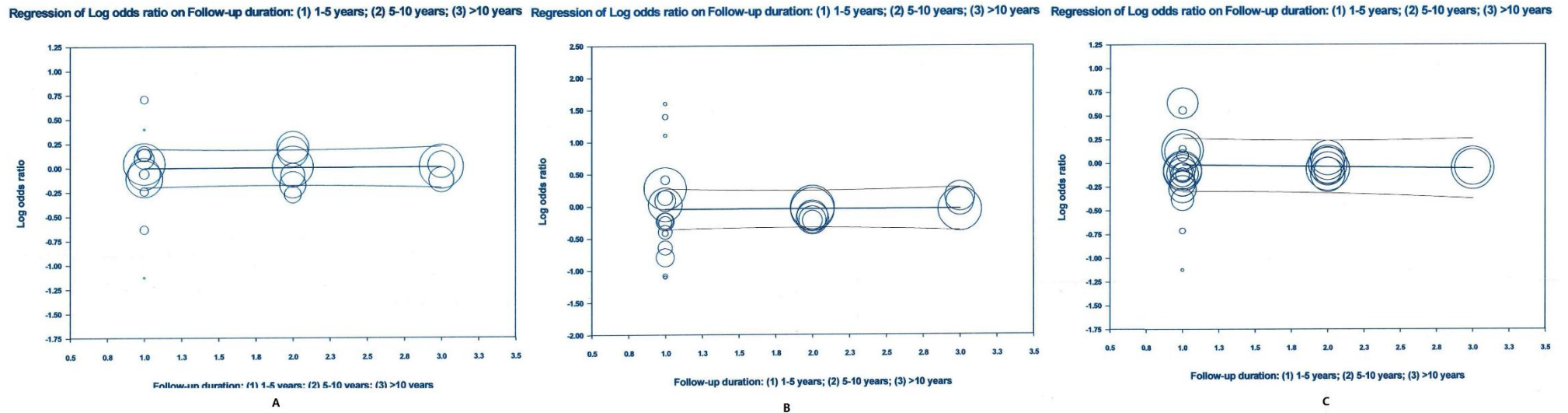
C

**Supplementary Figure 6.** Subgroup analysis based on follow-up duration showed that different follow-up durations (1-5 years, 5-10 years, or > 10 years) were not associated with significant reductions in total cancer incidence, cancer mortality and all-cause mortality. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

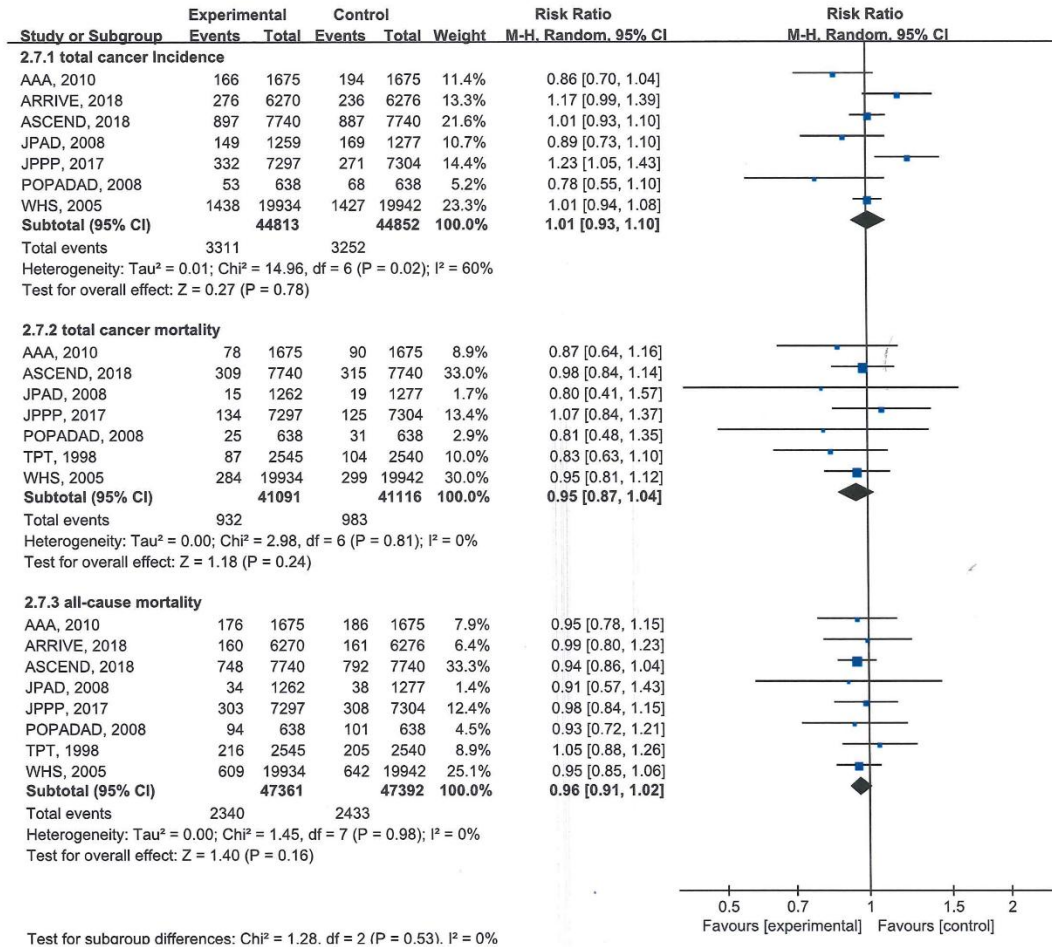




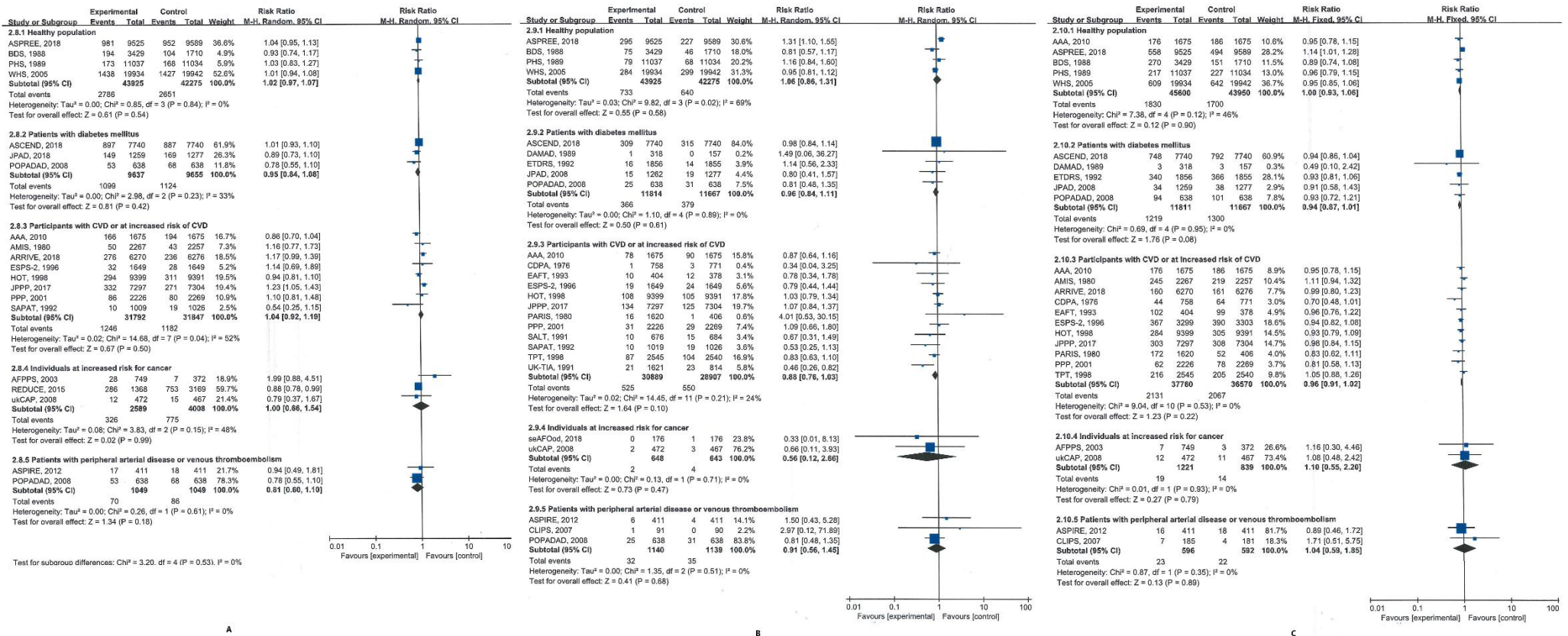
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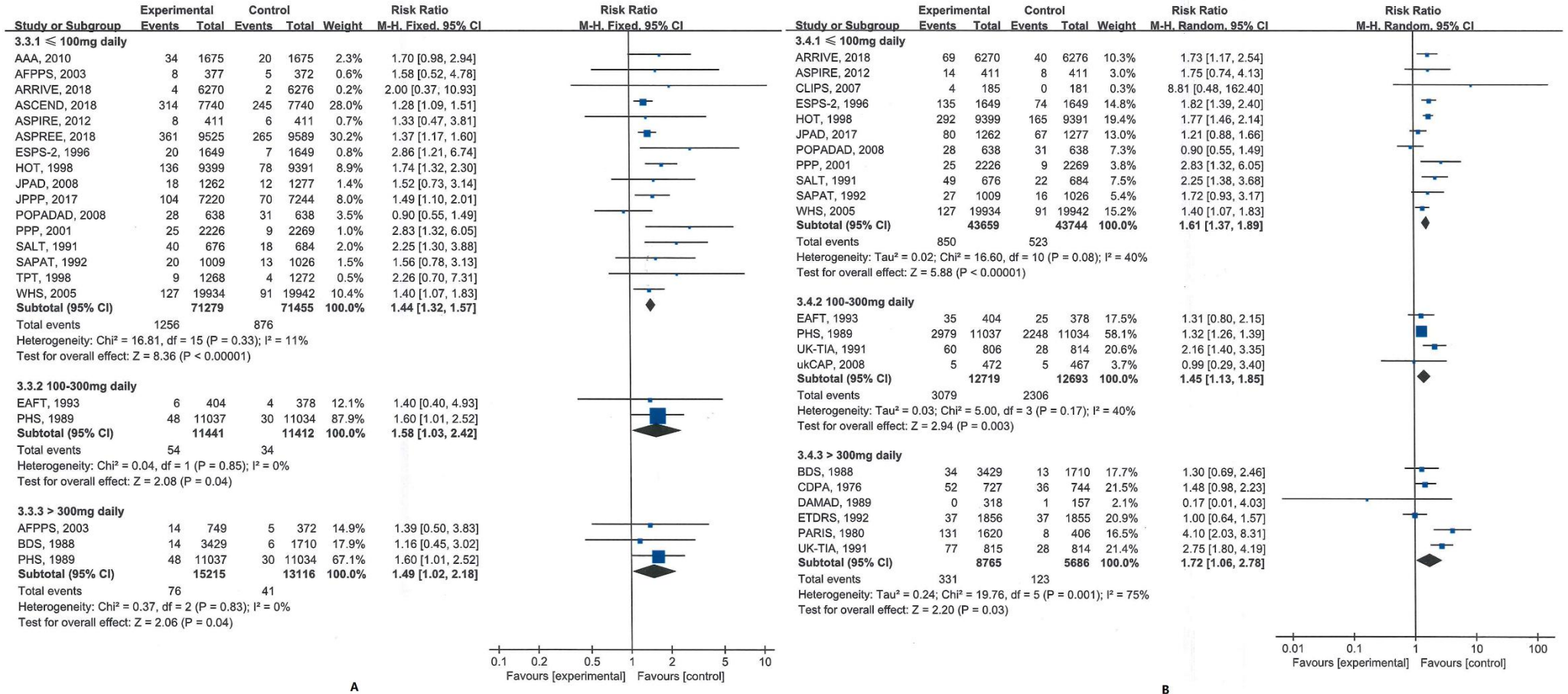
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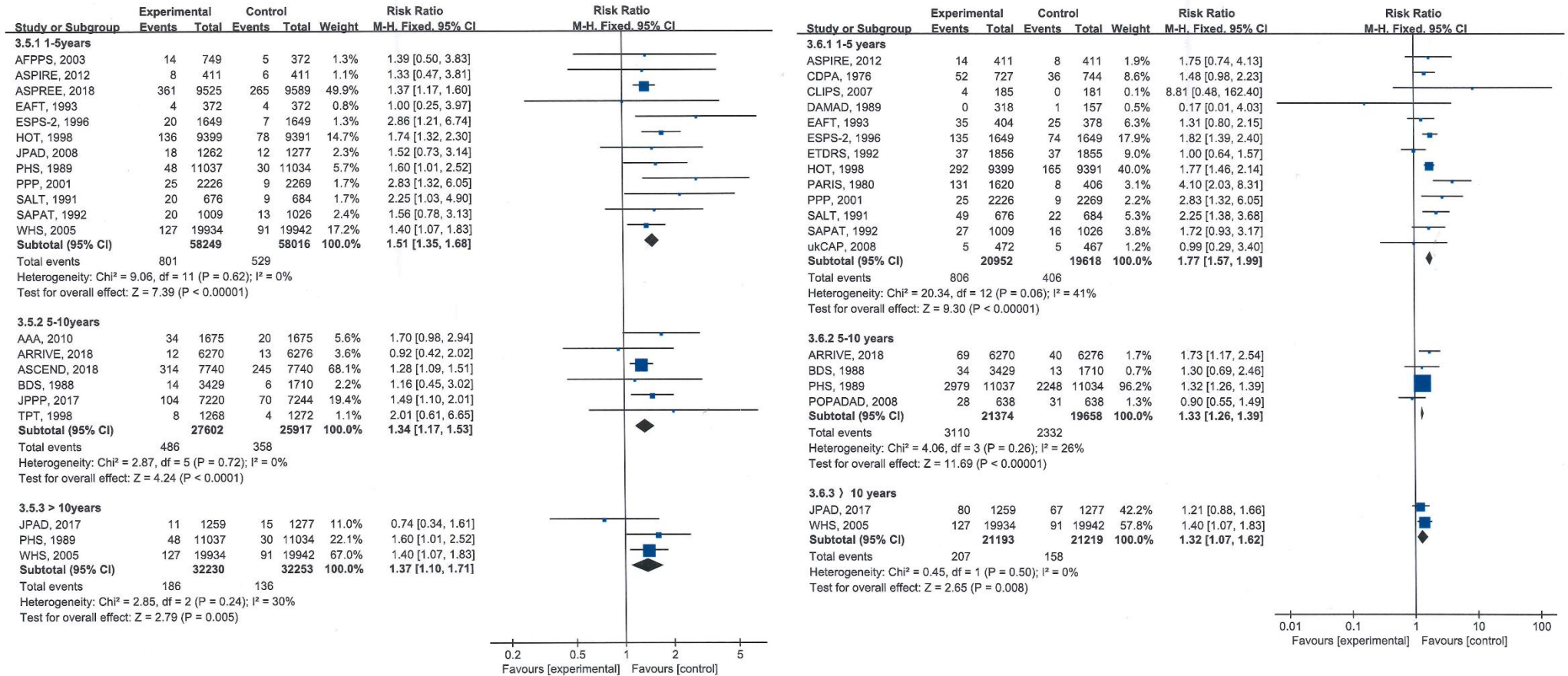
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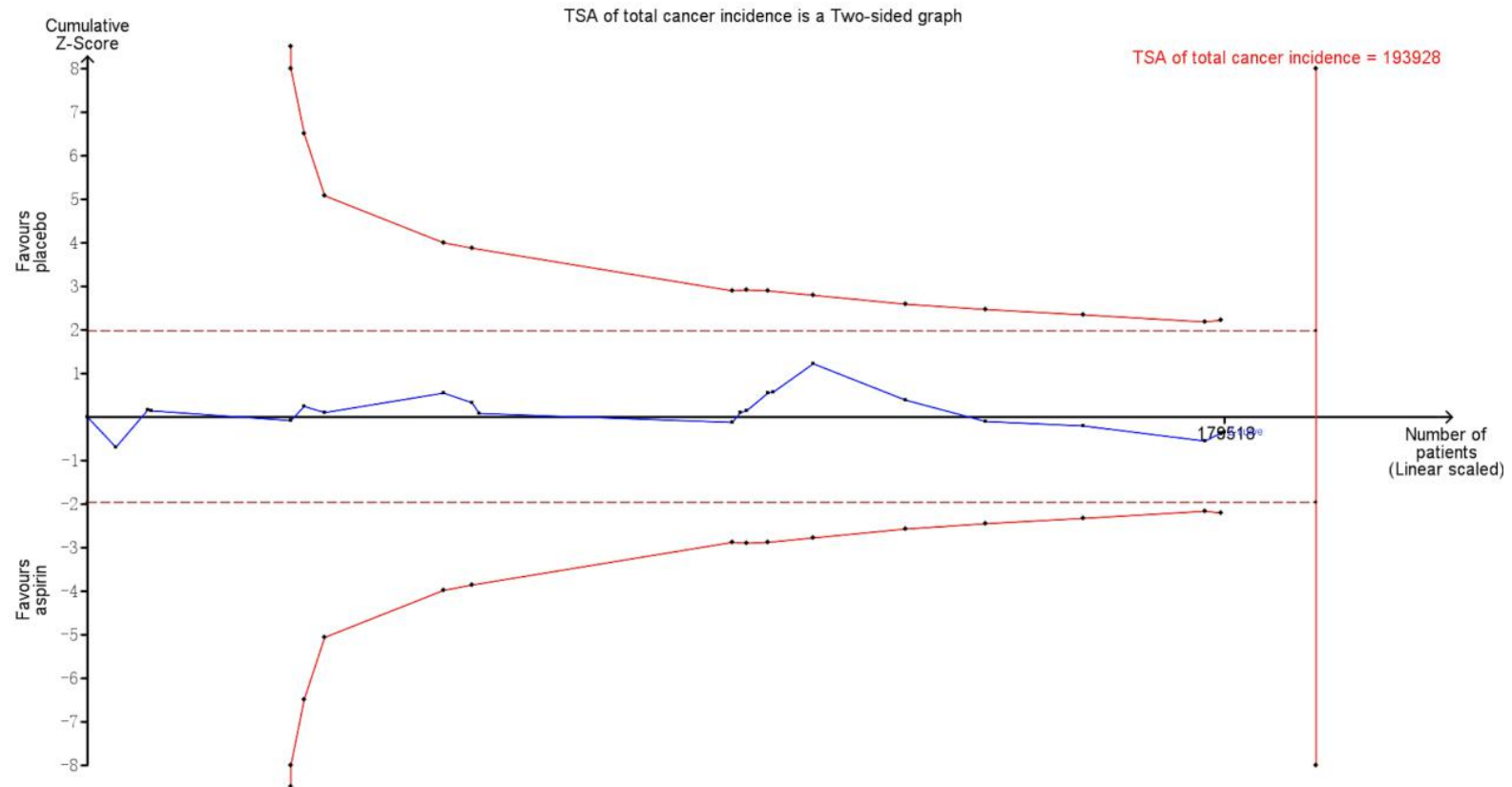
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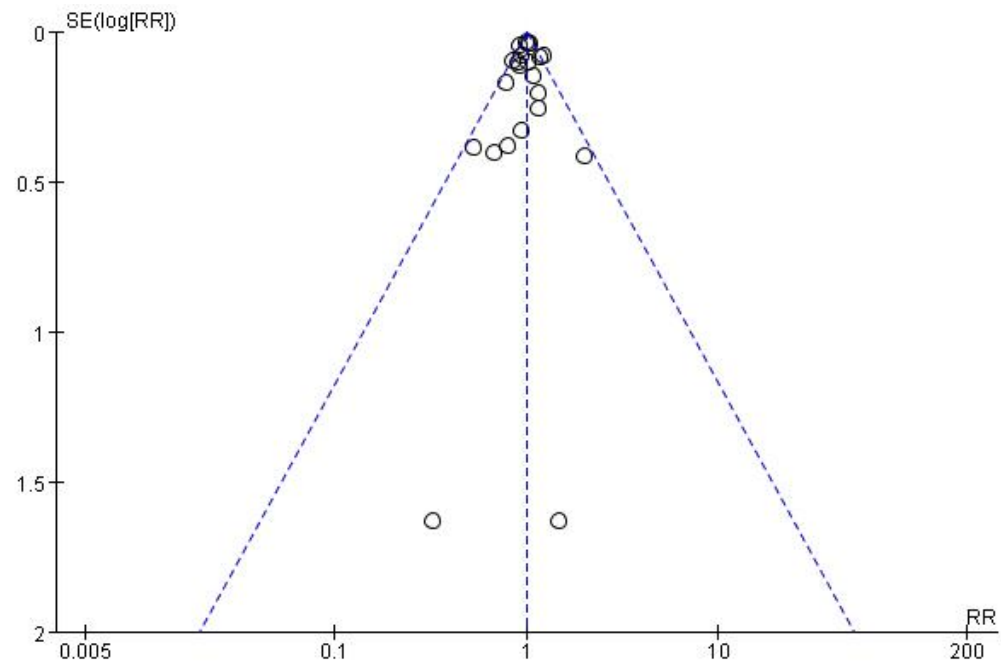
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**Supplementary Figure 13.** The funnel plots of total cancer incidence (the primary outcome).



**Supplementary Table 1:** The methodologic quality of the included trials assessed using the Cochrane risk of bias tool.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
AAA, 2010 <sup>1</sup>	+	+	+	+	+	+	?
AFPPS, 2003 <sup>2</sup>	+	+	+	+	+	+	?
AMIS, 1980 <sup>3</sup>	+	+	+	+	+	+	?
ARRIVE, 2018 <sup>4</sup>	+	+	+	+	+	+	?
ASCEND, 2018 <sup>5</sup>	+	+	+	+	+	+	?
ASPIRE, 2012 <sup>6</sup>	+	+	+	+	+	+	?
ASPREE, 2018 <sup>7</sup>	+	+	+	+	+	+	?
BDS, 1988 <sup>8</sup>	+	-	-	+	+	+	?
CDPA, 1980 <sup>9</sup>	+	+	+	+	+	+	?
CLIPS, 2007 <sup>10</sup>	+	+	+	+	+	+	?
DAMAD, 1989 <sup>11</sup>	+	+	+	+	+	+	?
EAFT, 1993 <sup>12</sup>	+	+	+	+	+	+	?
ESPS-2, 1996 <sup>13</sup>	+	+	+	+	+	+	?
ETDRS, 1992 <sup>14</sup>	+	+	+	+	+	+	?
HOT, 1998 <sup>15</sup>	+	+	+	+	+	+	?
JPAD, 2008 <sup>16</sup> / 2017 <sup>17</sup> /2018 <sup>18</sup>	+	-	-	+	+	+	?
JPPP, 2014 <sup>19</sup>	+	-	-	+	+	+	?
PARIS, 1980 <sup>20</sup>	+	+	+	+	+	+	?
PHS, 1989 <sup>21</sup> /1998 <sup>22</sup>	+	+	+	+	+	+	?
POPADAD, 2008 <sup>23</sup>	+	+	+	+	+	+	?
PPP, 2001 <sup>24</sup>	+	-	-	+	+	+	?
REDUCE, 2015 <sup>25</sup>	+	+	+	+	+	+	?
SALT, 1991 <sup>26</sup>	+	+	+	+	+	+	?
SAPAT, 1992 <sup>27</sup>	+	+	+	+	+	+	?
seAFOod, 2018 <sup>28</sup>	+	+	+	+	+	+	?
TPT, 1998 <sup>29</sup>	+	+	+	+	+	+	?
ukCAP, 2008 <sup>30</sup>	+	+	+	+	+	+	?
UK-TIA, 1991 <sup>31</sup>	+	+	+	+	+	+	?
WHS, 2005 <sup>32</sup>	+	+	+	+	+	+	?

+ = low risk of bias; ? = unclear risk of bias; - = high risk of bias.

**AAA**, Aspirin for Asymptomatic Atherosclerosis Trial; **AFPPS**, The Aspirin/Folate Polyp Prevention Study; **AMIS**, Aspirin Myocardial Infarction Study; **ARRIVE**, Aspirin to Reduce Risk of Initial Vascular Events; **ASCEND**, A Study of Cardiovascular Events in Diabetes; **ASPIRE**, Aspirin to Prevent Recurrent Venous Thromboembolism trial; **ASPREE**, Aspirin in Reducing Events in the Elderly; **BDS**, British Doctors Study; **CDPA**, Coronary Drug Project Research; **CLIPS**, Critical Leg Ischaemia Prevention Study; **DAMAD**, the Dipyridamole Aspirin Microangiopathy of Diabetes study; **EAFT**, European atrial fibrillation trial; **ESPS-2**, European Stroke Prevention Study 2; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **HOT**, Hypertension Optimal Treatment; **JPAD**, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; **JPPP**, Japanese Primary Prevention Project; **PARIS**, The Persantine-Aspirin Reinfarction Study; **PHS**, Physicians' Health Study; **POPADAD**, Prevention of Arterial Disease and Diabetes; **PPP**, Primary Prevention Project; **REDUCE**, the Reduction by Dutasteride of Prostate Cancer Events study; **SAPAT**, The Swedish Angina Pectoris Aspirin Trial; **SALT**, Swedish Aspirin Low-dose Trial; **seAFOod**, The Systematic Evaluation of Aspirin and Fish Oil Polyp Prevention Trial; **TPT**, Thrombosis Prevention Trial; **ukCAP**, The United Kingdom Colorectal Adenoma Prevention; **UK-TIA**, The United Kingdom transient ischaemic attack; **WHS**, Women's Health Study.



**Supplementary Table 2: GRADE evidence profile : long-term aspirin use for cancer primary prevention**

Indicators (Trials)		Quality assessment					Summary of findings					
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	No. of patients		Relative risk (95% CI)	Absolute effects	Quality	
							Aspirin	No aspirin		Risk difference (95% CI)		
Total cancer incidence (21)		No serious <sup>a</sup>	No serious	No serious	No serious	Undetected	5622/89673 (6.27%)	6001/89845 (6.68%)	1.01 (0.97 to 1.04) <sup>#</sup>	4 fewer per 1000 (-6 to -2)	⊕⊕⊕⊕ High	
Total cancer mortality (25)		No serious <sup>a</sup>	No serious	No serious	No serious	Undetected	1634/88020 (1.86%)	1577/84224 (1.87%)	1.00 (0.93 to 1.07) <sup>#</sup>	0 more per 1000 (-1 to 1)	⊕⊕⊕⊕ High	
All-cause mortality (28)		No serious <sup>a</sup>	No serious	No serious	No serious	Undetected	5225/97303 (5.37%)	4927/93129 (5.29%)	0.98 (0.94 to 1.02) <sup>#</sup>	1 more per 1000 (-1 to 3)	⊕⊕⊕⊕ High	
Major bleeding events (18)		No serious <sup>a</sup>	No serious	No serious	No serious	Undetected	1288/85851 (1.49%)	887/83933 (1.05%)	1.44 (1.32 to 1.57) <sup>#</sup>	4 more per 1000 (3 to 5)	⊕⊕⊕⊕ High	
Total bleeding events (19)		No serious <sup>b</sup>	Serious <sup>c</sup>	No serious	No serious	Undetected	4123/63519 (6.49%)	2896/60495 (4.79%)	1.52 (1.33 to 1.74) <sup>*</sup>	17 more per 1000 (15 to 20)	⊕⊕⊕⊕O Moderate	
<b>Subgroup analyses</b>												
Total cancer incidence	Dose of aspirin	≤ 100mg daily (15)	No serious	No serious	No serious	No serious	Undetected	4920/80446 (6.12%)	4835/80593 (6.00%)	1.02 (0.98 to 1.06) <sup>#</sup>	1 more per 1000 (-1 to 4)	⊕⊕⊕⊕ High
		100-300mg daily (2)	No serious	No serious	No serious	No serious	Undetected	185/11509 (1.61%)	183/11501 (1.59%)	1.01 (0.82 to 1.24) <sup>#</sup>	0 more per 1000 (-3 to 3)	⊕⊕⊕⊕ High
		> 300mg daily (3)	No serious	No serious	No serious	No serious	Undetected	256/6068 (4.22%)	154/4349 (3.54%)	1.01 (0.83 to 1.23) <sup>#</sup>	7 more per 1000 (-1 to 14)	⊕⊕⊕⊕ High
	Follow-up duration	1-5 years (12)	No serious	No serious	No serious	No serious	Undetected	1944/30394 (6.40%)	2477/32249 (7.68%)	0.99 (0.93 to 1.05) <sup>*</sup>	13 fewer per 1000 (-17 to -9)	⊕⊕⊕⊕ High
		5-10 years (6)	No serious	Serious <sup>c</sup>	No serious	No serious	Undetected	1918/27049 (7.09%)	1706/25343 (6.73%)	1.01 (0.90 to 1.14) <sup>*</sup>	2 more per 1000 (-3 to 6)	⊕⊕⊕⊕O Moderate
		>10 years (3)	No serious	No serious	No serious	No serious	Undetected	1760/32230 (5.46%)	1764/32253 (5.47%)	1.00 (0.94 to 1.06) <sup>*</sup>	0 fewer per 1000 (-4 to 3)	⊕⊕⊕⊕ High
	Study populations	Healthy population (4)	No serious	No serious	No serious	No serious	Undetected	2786/43925 (6.34%)	2651/42275 (6.27%)	1.02 (0.97 to 1.07) <sup>*</sup>	1 more per 1000 (-3 to 4)	⊕⊕⊕⊕ High
		With DM (3)	No serious	No serious	No serious	No serious	Undetected	1099/9637 (11.40%)	1124/9655 (11.64%)	0.95 (0.84 to 1.08) <sup>*</sup>	2 fewer per 1000 (-11 to 7)	⊕⊕⊕⊕ High
		With CVD or at increased risk of CVD (8)	No serious	Serious <sup>c</sup>	No serious	No serious	Undetected	1246/31972 (3.92%)	1182/31847 (3.71%)	1.04 (0.92 to 1.19) <sup>*</sup>	2 more per 1000 (-1 to 5)	⊕⊕⊕⊕O Moderate
		At increased risk of cancer (3)	No serious	No serious	No serious	No serious	Undetected	326/2589 (12.59%)	775/4008 (19.34%)	1.00 (0.66 to 1.54) <sup>*</sup>	67 fewer per 1000 (-85 to -50)	⊕⊕⊕⊕ High
		With peripheral arterial disease or venous thromboembolism (2)	No serious	No serious	No serious	No serious	Undetected	70/1049 (6.67%)	86/1049 (8.20%)	0.81 (0.60 to 1.10) <sup>*</sup>	15 fewer per 1000 (-38 to 7)	⊕⊕⊕⊕ High
		≤ 100mg daily (15)	No serious	No serious	No serious	No serious	Undetected	1413/66181 (2.14%)	1406/66316 (2.12%)	1.01 (0.94 to 1.08) <sup>#</sup>	0 more per 1000 (-1 to 2)	⊕⊕⊕⊕ High
Total cancer mortality	Dose of aspirin	100-300mg daily (5)	No serious	No serious	No serious	No serious	Undetected	112/12895 (0.87%)	107/12869 (0.83%)	1.04(0.80 to 1.35) <sup>#</sup>	0 more per 1000 (-2 to 3)	⊕⊕⊕⊕ High
		> 300mg daily(6)	No serious	No serious	No serious	No serious	Undetected	120/8796 (1.36%)	77/5713 (1.35%)	0.91 (0.68 to 1.22) <sup>#</sup>	0 more per 1000 (-4 to 4)	⊕⊕⊕⊕ High
		1-5 years (17)	No serious	No serious	No serious	No serious	Undetected	563/33416 (1.68%)	499/31501 (1.58%)	1.08 (0.96 to 1.22) <sup>#</sup>	1 more per 1000 (-1 to 3)	⊕⊕⊕⊕ High
	Follow-up duration	5-10 years (6)	No serious	No serious	No serious	No serious	Undetected	858/35961 (1.05%)	885/34245 (2.58%)	0.92 (0.84 to 1.01) <sup>#</sup>	2 fewer per 1000 (-4 to 0)	⊕⊕⊕⊕ High

		>10 years (3)	No serious	No serious	No serious	No serious	Undetected	426/32230 (1.17%)	427/32253 (1.32%)	1.00 (0.88 to 1.14) <sup>#</sup>	0 fewer per 1000 (-2 to 2)	⊕⊕⊕⊕ High	
	Study populations	Healthy population (4)	No serious	Serious <sup>c</sup>	No serious	No serious	Undetected	733/43925 (1.67%)	640/42275 (1.51%)	1.06 (0.86 to 1.31) <sup>*</sup>	2 more per 1000 (0 to 3)	⊕⊕⊕⊕ Moderate	
		With DM (5)	No serious	No serious	No serious	No serious	Undetected	366/11814 (3.10%)	379/11667 (3.25%)	0.96 (0.84 to 1.11) <sup>*</sup>	1 fewer per 1000 (-6 to 4)	⊕⊕⊕⊕ High	
		With CVD or at increased risk of CVD (12)	No serious	No serious	No serious	No serious	Undetected	525/30889 (1.70%)	550/28907 (1.90%)	0.88 (0.76 to 1.03) <sup>*</sup>	2 fewer per 1000 (-4 to 1)	⊕⊕⊕⊕ High	
		At increased risk of cancer (2)	No serious	No serious	No serious	No serious	Undetected	2/648 (0.31%)	4/643 (0.62%)	0.56 (0.12 to 2.66) <sup>*</sup>	3 fewer per 1000 (-11 to 4)	⊕⊕⊕⊕ High	
		With peripheral arterial disease or venous thromboembolism (3)	No serious	No serious	No serious	No serious	Undetected	32/1140 (2.81%)	35/1139 (3.07%)	0.91 (0.56 to 1.45) <sup>*</sup>	3 fewer per 1000 (-17 to 11)	⊕⊕⊕⊕ High	
			≤ 100mg daily (18)	No serious	No serious	No serious	No serious	Undetected	3997/85512 (4.67%)	4127/85652 (4.82%)	0.97 (0.93 to 1.01) <sup>#</sup>	1 fewer per 1000 (-4 to 1)	⊕⊕⊕⊕ High
	Dose of aspirin	100-300mg daily (5)	No serious	No serious	No serious	No serious	Undetected	440/13043 (3.37%)	460/13009 (3.54%)	0.94 (0.83 to 1.07) <sup>#</sup>	2 fewer per 1000 (-6 to 3)	⊕⊕⊕⊕ High	
		> 300mg daily (8)	No serious	No serious	No serious	No serious	Undetected	1190/11435 (10.41%)	980/8342 (11.75%)	0.94 (0.86 to 1.01) <sup>#</sup>	13 less per 1000 (-22 to -5)	⊕⊕⊕⊕ High	
	Follow-up duration	1-5 years (19)	No serious	Serious <sup>c</sup>	No serious	No serious	Undetected	2432/36741 (6.76%)	2154/34270 (6.59%)	0.97 (0.88 to 1.08) <sup>*</sup>	4 more per 1000 (0 to 7)	⊕⊕⊕⊕ Moderate	
		5-10 years (7)	No serious	No serious	No serious	No serious	Undetected	1967/29549 (6.65%)	1904/27883 (6.41%)	0.96 (0.90 to 1.02) <sup>*</sup>	2 fewer per 1000 (-6 to 2)	⊕⊕⊕⊕ High	
		>10 years (2)	No serious	No serious	No serious	No serious	Undetected	826/30971 (2.67%)	869/30976 (2.81%)	0.95 (0.87 to 1.04) <sup>*</sup>	1 fewer per 1000 (-4 to 1)	⊕⊕⊕⊕ High	
All-cause mortality	Study populations	Healthy population (5)	No serious	No serious	No serious	No serious	Undetected	1830/45600 (4.00%)	1700/43950 (3.90%)	1.00 (0.93 to 1.06) <sup>#</sup>	2 more per 1000 (-1 to 4)	⊕⊕⊕⊕ High	
		With DM (5)	No serious	No serious	No serious	No serious	Undetected	1219/11811 (10.32%)	1300/11667 (11.14%)	0.94 (0.87 to 1.01) <sup>#</sup>	8 fewer per 1000 (-16 to 0)	⊕⊕⊕⊕ High	
		With CVD or at increased risk of CVD (11)	No serious	No serious	No serious	No serious	Undetected	2131/37760 (5.64%)	2067/36570 (5.65%)	0.96(0.91 to 1.02) <sup>#</sup>	0 fewer per 1000 (-3 to 3)	⊕⊕⊕⊕ High	
		At increased risk of cancer (2)	No serious	No serious	No serious	No serious	Undetected	19/1221 (1.56%)	14/839 (1.67%)	1.10 (0.55 to 2.20) <sup>#</sup>	1 fewer per 1000 (-12 to 10)	⊕⊕⊕⊕ High	
		With peripheral arterial disease or venous thromboembolism (2)	No serious	No serious	No serious	No serious	Undetected	23/596 (3.86%)	22/592 (3.72%)	1.04 (0.59 to 1.85) <sup>#</sup>	1 more per 1000 (-20 to 23)	⊕⊕⊕⊕ High	
			Aspirin ≤ 100mg/d for more than five years	No serious	Serious <sup>c</sup>	No serious	No serious	Undetected	3311/44813 (7.39%)	3252/44852 (7.25%)	1.01 (0.93 to 1.10) <sup>*</sup>	1 more per 1000 (-2 to 5)	⊕⊕⊕⊕ Moderate
Total cancer incidence (7)	Dose of aspirin and Follow-up duration	Aspirin ≤ 100mg/d for more than five years	No serious	No serious	No serious	No serious	Undetected	932/41091 (2.27%)	983/41116 (2.49%)	0.95 (0.87 to 1.04) <sup>*</sup>	1 fewer per 1000 (-3 to 1)	⊕⊕⊕⊕ High	
Total cancer mortality (7)			No serious	No serious	No serious	No serious	Undetected	2340/47361 (4.94%)	2433/47392 (5.13%)	0.96 (0.91 to 1.02) <sup>*</sup>	2 fewer per 1000 (-5 to 1)	⊕⊕⊕⊕ High	
All-cause mortality (8)	Major bleeding events	Dose of aspirin	≤ 100mg daily (16)	No serious	No serious	No serious	No serious	Undetected	1256/71279 (1.75%)	876/71455 (1.22%)	1.44 (1.32 to 1.57) <sup>#</sup>	5 more per 1000 (4 to 7)	⊕⊕⊕⊕ High
			100-300mg daily (2)	No serious	No serious	No serious	No serious	Undetected	54/11441 (0.47%)	34/11412 (0.30%)	1.58 (1.03 to 2.42) <sup>#</sup>	2 more per 1000 (0 to 3)	⊕⊕⊕⊕ High
			> 300mg daily(3)	No serious	No serious	No serious	No serious	Undetected	76/15215 (0.50%)	41/13116 (0.31%)	1.49 (1.02 to 2.18) <sup>#</sup>	2 more per 1000 (0 to 3)	⊕⊕⊕⊕ High
	Follow-up duration	1-5 years (12)	No serious	No serious	No serious	No serious	Undetected	801/58249 (1.38%)	529/58016 (9.11%)	1.51 (1.35 to 1.69) <sup>#</sup>	5 more per 1000 (3 to 6)	⊕⊕⊕⊕ High	

Total bleeding events	Dose of aspirin	5-10 years (6)	No serious	No serious	No serious	No serious	Undetected	486/27602 (1.76%)	358/25917 (1.38%)	1.34 (1.17 to 1.53) <sup>#</sup>	4 more per 1000 (2 to 6)	⊕⊕⊕⊕ High
		>10 years (3)	No serious	No serious	No serious	No serious	Undetected	186/32230 (0.60%)	136/32253 (0.41%)	1.37 (1.17 to 1.81)	2 more per 1000 (1 to 3)	⊕⊕⊕⊕ High
		≤ 100mg daily (11)	No serious	No serious	No serious	No serious	Undetected	850/43659 (1.94%)	523/43744 (1.19%)	1.61 (1.37 to 1.89) <sup>*</sup>	13 more per 1000 (10 to 15)	⊕⊕⊕⊕ High
		100-300mg daily (4)	No serious	No serious	No serious	No serious	Undetected	3079/12719 (24%)	2306/12693 (18.17%)	1.45 (1.13 to 1.85) <sup>*</sup>	60 more per 1000 (50 to 70)	⊕⊕⊕⊕ High
	> 300mg daily(6)	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	331/8765 (3.78%)	123/5686 (2.16%)	1.72 (1.06 to 2.78) <sup>*</sup>	16 more per 1000 (10 to 22)	⊕⊕⊕O Moderate	
	Follow-up duration	1-5 years (13)	No serious	No serious	No serious	No serious	Undetected	806/21374 (3.85%)	406/19618 (2.07%)	1.77 (1.57 to 1.99) <sup>#</sup>	15 more per 1000 (15 to 21)	⊕⊕⊕⊕ High
		5-10 years (4)	No serious	No serious	No serious	No serious	Undetected	3110/23919 (13.00%)	2332/19658 (11.86%)	1.33 (1.26 to 1.39) <sup>#</sup>	27 more per 1000 (20 to 33)	⊕⊕⊕⊕ High
		>10 years (2)	No serious	No serious	No serious	No serious	Undetected	207/21193 (0.98%)	158/21219 (0.74%)	1.32 (1.07 to 1.62) <sup>#</sup>	2 more per 1000 (1 to 4)	⊕⊕⊕⊕ High

Note: CVD: cardiovascular diseases; DM: diabetes mellitus; and CI: confidence interval. <sup>#</sup> fixed-effects model, <sup>\*</sup> random-effects model.

<sup>a</sup> 4 trials, <sup>b</sup> 3 trials, <sup>c</sup> 1 trials, or <sup>d</sup> 2 trials were open-labelled and end-point blinded, most trials were low risk, the result had good robustness, and the evidence was not rated down; <sup>e</sup> heterogeneity occurred in them, the result had good robustness, and the evidence was rated down by one level.

**Supplementary Table 3: Sensitivity analyses**

<b>Outcome</b>	<b>Double-blind, placebo- controlled studies</b> [Study number; subject size; RR (95% CI); <i>P</i> value]	<b>Subject size</b> (≥ 2,000 in each group) [Study number; subject size; RR (95% CI); <i>P</i> value]	<b>Studies published</b> since the year 2000 [Study number; subject size; RR (95% CI); <i>P</i> value]	<b>Excluding studies enrolling patients</b> with increased risk of cancer [Study number; subject size; RR (95% CI); <i>P</i> value]
<b>Efficacy</b>				
Total cancer incidence	17 studies; N=152,747; 1.00(0.96 to 1.04); <i>P</i> =0.96	11 studies; N=156,636; 1.03 (0.99 to 1.07); <i>P</i> =0.10	14 studies; N=123,186; 1.01 (0.97 to 1.05); <i>P</i> =0.55	18 studies; N=176,818; 1.00 (0.97 to 1.04); <i>P</i> =0.31
Total cancer mortality	21 studies; N=145,470; 1.00 (0.93 to 1.07); <i>P</i> =0.95	9 studies; N=144,651; 1.03 (0.96 to 1.11); <i>P</i> =0.37	12 studies; N=103,498; 1.04 (0.96 to 1.12); <i>P</i> =0.39	23 studies; N=170,662; 1.00 (0.93 to 1.07); <i>P</i> =0.93
All-cause mortality	24 studies; N=163,661 0.99 (0.95 to 1.03); <i>P</i> =0.56	12 studies; N=165,432; 0.98 (0.94 to 1.02); <i>P</i> =0.39	13 studies; N=77,286; 0.99 (0.94 to 1.05); <i>P</i> =0.80	25 studies; N=187,732; 0.98 (0.94 to 1.02); <i>P</i> =0.31
<b>Safety</b>				
Major bleeding events	14 studies; N=145,692; 1.42(1.30 to 1.55); <i>P</i> <0.00001	10 studies; N=157,060; 1.41(1.29 to 1.54); <i>P</i> <0.00001	10 studies; N=114,077; 1.38 (1.25 to 1.51); <i>P</i> <0.00001	17 studies; N=171,208; 1.44(1.32 to 1.56); <i>P</i> <0.00001
Total bleeding events	17 studies; N=116,929; 1.35(1.31 to 1.40); <i>P</i> <0.00001	7 studies; N=108,002; 1.34(1.29 to 1.39); <i>P</i> <0.00001	8 studies; N=62,856; 1.41(1.20 to 1.65); <i>P</i> <0.0001	19 studies; N=128,160; 1.36(1.31 to 1.41); <i>P</i> <0.00001

**RR**, Risk Ratio, **CI**: confidence interval; **N**, the number of participants included in each analysis.

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