### 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  $\leq 100 \text{ mg to} > 300 \text{ mg}$ ). 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 ( $\leq 100 \text{ mg/day}$ ) 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 ( $\leq 100 \text{ mg}$ , 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.

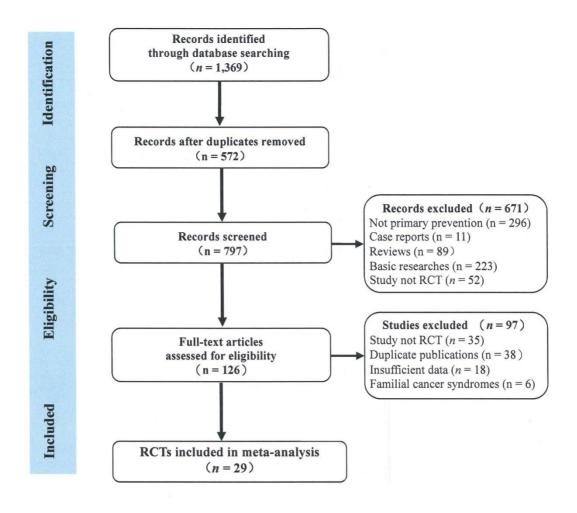
Supplementary Figure 13. The funnel plots of total cancer incidence (the primary outcome).

**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.

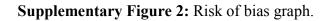
Supplementary Table 3. Sensitivity analyses.

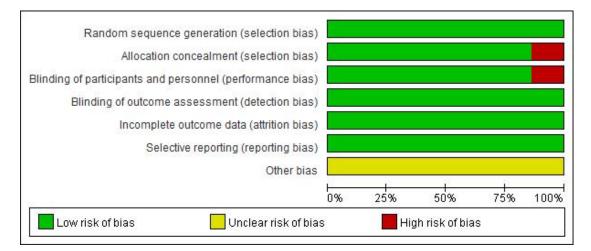
### Supplementary Figure 1: PRISMA diagram of searching

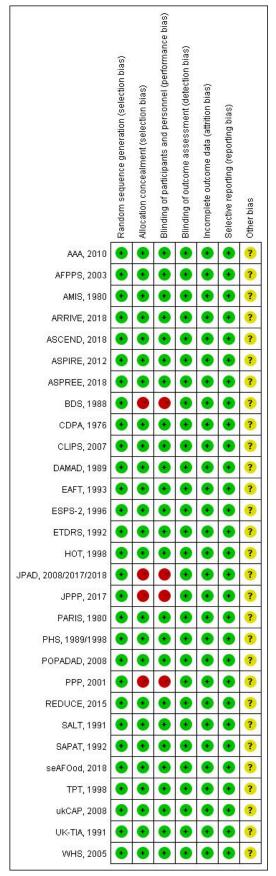


RCT, randomised controlled trial;

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







## Supplementary Figure 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

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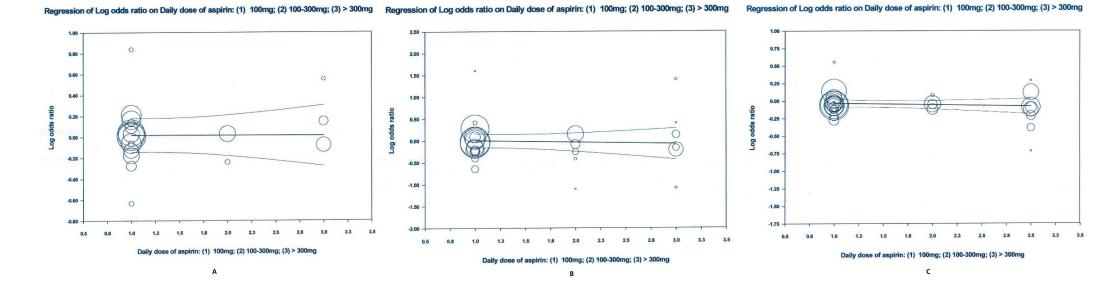
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in total cancer incidence, total cancer mortality, or all-cause mortality. A) Total cancer incidence, B) total cancer mortality, C) all-cause mortality.

											Experimental			<b>Risk Ratio</b>	Risk Ratio
										Study or Subgroup		al Events	Total Weight	M-H, Fixed, 95% CI	M-H. Fixed, 95% Cl
										2.3.1 ≤ 100mg daily					
						Experimental	Control	Risk Ratio	Risk Ratio	SAPAT, 1992	82 101	19 106	1026 2.6%	0.78 [0.59, 1.03]	-
					Study or Subgroup	Events Total	Events Total Weight	M-H, Fixed, 95% CI	M-H. Fixed, 95% Cl	PPP, 2001	62 222	26 78	2269 1.9%	0.81 [0.58, 1.13]	
	Experimental	Control	Risk Ratio	Risk Ratio	2.2.1 ≤ 100mg daily					ASPIRE, 2012	16 41		411 0.4%	0.89 [0.46, 1.72]	
Study or Subgroup E	Events Total	Events Total Weight	M-H. Fixed, 95% Cl	M-H. Fixed. 95% Cl	AAA, 2010	78 1675	90 1675 6.4%	0.87 [0.64, 1.16]		SALT, 1991	61 67		684 1.7%	0.89 [0.64, 1.24]	
2.1.1 ≤ 100mg daily					ASCEND, 2018	309 7740	315 7740 22.4%	0.98 [0.84, 1.14]	+	JPAD, 2008	34 126		1277 0.9%	0.91 [0.57, 1.43]	-
AAA, 2010	166 1675	194 1675 4.0%	0.86 [0.70, 1.04]		ASPIRE, 2012	6 411	4 411 0.3%	1.50 [0.43, 5.28]		HOT, 1998	284 939	99 305	9391 7.4%	0.93 [0.79, 1.09]	1
AFPPS, 2003	16 377	7 372 0.1%	2.26 [0.94, 5.42]		ASPREE, 2018	295 9525	227 9589 16.1%	1.31 [1.10, 1.55]	*	POPADAD, 2008	94 63	38 101	638 2.4%	0.93 [0.72, 1.21]	-
ARRIVE, 2018	276 6270	236 6276 4.9%			CLIPS, 2007	2 185	0 181 0.0%	4.89 [0.24, 101.21]		ESPS-2, 1996	367 329			0.94 [0.82, 1.08]	1
ASCEND, 2018	897 7740	887 7740 18.4%		Ť	ESPS-2, 1996	19 1649	24 1649 1.7%	0.79 [0.44, 1.44]		ASCEND, 2018	748 774			0.94 [0.86, 1.04]	
ASPIRE, 2012	17 411	18 411 0.4%			HOT, 1998	108 9399	105 9391 7.5%	1.03 [0.79, 1.34]	+	AAA, 2010	176 167			0.95 [0.78, 1.15]	1
ASPREE, 2018	981 9525	952 9589 19.6%			JPAD, 2008	15 1262	19 1277 1.3%	0.80 [0.41, 1.57]		WHS, 2005	609 1993			0.95 [0.85, 1.06]	1
ESPS-2, 1996	32 1649	28 1649 0.6%			JPPP, 2017	134 7297	125 7304 8.9%	1.07 [0.84, 1.37]	*	PHS, 1989	217 1103			0.96 [0.79, 1.15]	T
HOT, 1998	294 9399	311 9391 6.4%			POPADAD, 2008	25 638	31 638 2.2%	0.81 [0.48, 1.35]		JPPP, 2017	303 729			0.98 [0.84, 1.15]	
JPAD, 2018	149 1259	169 1277 3.5%			PPP, 2001	31 2226	29 2269 2.0%	1.09 [0.66, 1.80]		AFPPS, 2003	3 3			0.99 [0.20, 4.86]	
JPPP, 2017	332 7297	271 7304 5.6%			SALT, 1991	10 676	15 684 1.1%	0.67 [0.31, 1.49]		ARRIVE, 2018	160 623			0.99 [0.80, 1.23]	
PHS, 1989	173 11037	168 11034 3.5%			SAPAT, 1992	10 1019	19 1026 1.3%	0.53 [0.25, 1.13]		TPT, 1998	216 25			1.05 [0.88, 1.26]	Ľ
POPADAD, 2008	53 638	68 638 1.4%			TPT, 1998	87 2545	104 2540 7.4%	0.83 [0.63, 1.10]		ASPREE, 2018	558 953			1.14 [1.01, 1.28]	
PPP, 2001	86 2226	80 2269 1.6%			WHS, 2005	284 19934		0.95 [0.81, 1.12]	1	CLIPS, 2007	7 1		181 0.1%	1.71 [0.51, 5.75]	
SAPAT, 1992	10 1009	19 1026 0.4%			Subtotal (95% CI)	66181	66316 100.0%	1.01 [0.94, 1.08]	1	Subtotal (95% CI)				0.97 [0.93, 1.01]	
WHS, 2005 Subtotal (95% CI)	1438 19934 80446	1427 19942 29.5%	1.01 [0.94, 1.08] 1.02 [0.98, 1.06]	T	Total events	1413	1406			Total events	3997	4127			
	4920	4835	1.02 [0.96, 1.06]		Heterogeneity: Chi <sup>2</sup> = 1					Heterogeneity: Chi <sup>2</sup> = Test for overall effect:			= 0%		
Total events Heterogeneity: Chi <sup>2</sup> = 22.					Test for overall effect: 2	2 = 0.19 (P = 0.85)	)			Test for overall effect	2 = 1.41 (P = 0.)	10)			
Test for overall effect: Z =					2.2.2 100-300mg daily					2.3.2 100-300mg dai	h.,				
Test for overall effect: 2 =	= 1.02 (P = 0.31)	)			EAFT, 1993	1000 00000	40 070 44 54			seAFOod, 2018	0 3	04 4	316 0.3%	0.33 [0.01, 7.95]	
2.1.2 100-300mg daily					PHS, 1989	10 404 79 11037	12 378 11.5%	0.78 [0.34, 1.78]		UK-TIA, 1991	109 8				-
PHS. 1989	173 11037	168 11034 91.8%	1.03 [0.83, 1.27]		seAFOod, 2018	0 176	68 11034 63.1% 1 176 1.4%			PHS, 1989	217 110			0.96 [0.79, 1.15]	-
ukCAP, 2008	12 472				UK-TIA, 1991	21 806	1 176 1.4% 23 814 21.2%	0.33 [0.01, 8.13] 0.92 [0.51, 1.65]		EAFT, 1993		04 99			Ŧ
Subtotal (95% CI)	11509		1.01 [0.82, 1.24]	•	ukCAP, 2008	2 472		0.66 [0.11, 3.93]		ukCAP, 2008	12 4				
Total events	185	183			Subtotal (95% CI)	12895	12869 100.0%			Subtotal (95% CI)	12 4		13009 100.0%		
Heterogeneity: Chi <sup>2</sup> = 0.4					Total events	112	107	1.04 [0.00, 1.00]	Ť	Total events	440	460		and format trail	1
Test for overall effect: Z =					Heterogeneity: Chi <sup>2</sup> = 1					Heterogeneity: Chi <sup>2</sup> =					
Test for evenue encour 2	- 0.10 (1 - 0.02)	,			Test for overall effect:					Test for overall effect					
2.1.3 > 300mg daily					reactor overall eneor.	x = 0.00 (i = 0.70)	,			Tool of oronal chool					
AFPPS, 2003	12 372	7 372 3.7%	1.71 [0.68, 4.31]		2.2.3 > 300mg daily					2.3.3 > 300mg daily					
AMIS, 1980	50 2267	43 2257 22.8%			BDS, 1988	75 3429	46 1710 65.6%	0.81 [0.57, 1.17]		DAMAD, 1989	3 3	18 3	157 0.4%	0.49 [0.10, 2.42]	
BDS, 1988	194 3429			-	CDPA, 1976	1 758	3 771 3.2%	0.34 [0.04, 3.25]		CDPA, 1976		58 64	771 6.0%	0.70 [0.48, 1.01]	
Subtotal (95% CI)	6068	4339 100.09		•	DAMAD, 1989	1 318		1.49 [0.06, 36.27]		PARIS, 1980	172 16			0.83 [0.62, 1.11]	
Total events	256	154			ETDRS, 1992	16 1856		1.14 [0.56, 2.33]		BDS, 1988	270 34	29 151	1710 19.0%	0.89 [0.74, 1.08]	+
Heterogeneity: Chi <sup>2</sup> = 2.1	19. df = 2 (P = 0.	33); l <sup>2</sup> = 9%			PARIS, 1980	16 1620		4.01 [0.53, 30.15]		UK-TIA, 1991		15 122		0.92 [0.72, 1.16]	+
Test for overall effect: Z =					UK-TIA, 1991	11 815		0.85 [0.38, 1.88]		ETDRS, 1992	340 18				
		·			Subtotal (95% CI)	8796		0.91 [0.68, 1.22]	*	AMIS, 1980	245 22		2257 20.7%		+
				0.2 0.5 1 2 5	Total events	120	77			AFPPS, 2003	4 3	72 3	372 0.3%	1.33 [0.30, 5.92]	
				0.2 0.5 1 2 5 Favours [experimental] Favours [control]	Heterogeneity: Chi <sup>2</sup> = 3	3.69, df = 5 (P = 0./	59); l <sup>2</sup> = 0%			Subtotal (95% CI)	114	35	8342 100.0%	0.94 [0.86, 1.01]	*
				Pavours (experimental) Pavours (control)	Test for overall effect:					Total events	1190	980			
										Heterogeneity: Chi <sup>2</sup> =	= 8.08, df = 7 (P =	= 0.33);  2 =	13%		
										Test for overall effect					
									0.01 0.1 1 10 100 Favours [experimental] Favours [control].						a a a a a a a a a a a a a a a a a a a
									Pavours (experimental) Pavours (control),						0.01 0.1 1 10 100
			A					B						c	Favours [experimental] Favours [control]
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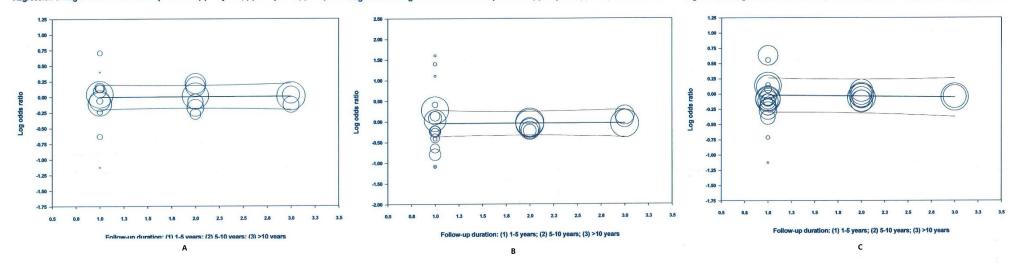
**Supplementary Figure 5.** The results of meta-regression analyses showing that the total cancer incidence, cancer mortality and all-cause mortality did not vary significantly with respect to the daily dose of aspirin (from  $\leq 100 \text{ mg}$  to >300 mg). A) Total cancer incidence, B) total cancer 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.

		Experimental Control Risk Ratio	Risk Ratio	Experimental Control Risk Ratio	Risk Ratio
		Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl	M-H. Fixed, 95% Cl	Study or Subgroup Events Total Events Total Weight M-H. Random. 95% Cl	M-H. Random, 95% Cl
Experimental Control	Risk Ratio Risk Ratio	2.5.1 1-5 years		2.6.1 1-5 years	
Study or Subgroup Events Total Events Total Weight M		ASPIRE, 2012 6 411 4 411 0.8% 1.50 [0.43, 5.28]		AFPPS, 2003 7 749 3 372 0.6% 1.16 [0.30, 4.46]	
2.4.1 1-5years	HE KANGON, 5576 CI	ASPREE, 2018 295 9525 227 9589 44.5% 1.31 [1.10, 1.55]		AMIS, 1980 245 2267 219 2257 9.0% 1.11 [0.94, 1.32]	+
AFPPS, 2003 28 749 7 372 0.5%	1.99 [0.88, 4.51]	CDPA, 1976 1 758 3 771 0.6% 0.34 [0.04, 3.25]		ASPIRE, 2012 16 411 18 411 2.1% 0.89 [0.46, 1.72]	
AMIS, 1980 50 2267 43 2257 2.2%	1.16 [0.77, 1.73]	CLIPS, 2007 2 185 0 181 0.1% 4.89 [0.24, 101.21]		ASPREE, 2018 558 9525 494 9589 10.3% 1.14 [1.01, 1.28]	-
ASPIRE, 2012 17 411 18 411 0.9%	0.94 (0.49, 1.81)	DAMAD, 1989 1 157 0 157 0.1% 3.00 [0.12, 73.08]		CDPA, 1976 44 758 64 771 4.9% 0.70 [0.48, 1.01]	
ASPREE, 2018 981 9525 952 9589 43.0%	1.04 (0.95, 1.13)	EAFT, 1993 10 404 12 378 2.4% 0.78 [0.34, 1.78]		CLIPS, 2007 7 185 4 181 0.7% 1.71 [0.51, 5.75]	
DAMAD, 1989 1 318 0 157 0.0%	1.49 [0.06, 36.27]	ESPS-2, 1996 19 1649 24 1649 4.7% 0.79 [0.44, 1.44]		DAMAD, 1989 3 318 3 157 0.4% 0.49 [0.10, 2.42]	
ESPS-2, 1996 32 1649 28 1649 1.4%	1.14 [0.69, 1.89]	ETDRS, 1992 16 1856 14 1855 2.8% 1.14 [0.56, 2.33]		EAFT, 1993 102 404 99 378 7.4% 0.96 [0.76, 1.22]	*
HOT, 1998 294 9399 311 9391 14,1%	0.94 [0.81, 1,10]	HOT, 1998 108 9399 105 9391 20.7% 1.03 [0.79, 1.34]	+	ESPS-2, 1996 182 1649 102 1649 7.6% 1.78 [1.41, 2.25]	-
PPP, 2001 86 2226 80 2269 4.0%	1.10 [0.81, 1.48]	JPAD, 2008 15 1262 19 1277 3.7% 0.80 [0.41, 1.57]		ETDRS, 1992 340 1856 366 1855 10.0% 0.93 [0.81, 1.06]	-
REDUCE 2015 433 2045 1003 4345 32.4%	0.92 [0.83, 1.01]	PARIS, 1980 16 1620 1 406 0.3% 4.01 [0.53, 30.15]		HOT, 1998 284 9399 305 9391 9.3% 0.93 [0.79, 1.09]	*
SAPAT, 1992 10 1009 19 1026 0.6%	0.54 [0.25, 1.15]	PPP, 2001 31 2226 29 2269 5.7% 1.09 [0.66, 1.80]		JPAD, 2008 34 1262 38 1277 3.7% 0.91 [0.57, 1.43]	
seAFOod. 2018 0 324 1 316 0.0%	0.33 [0.01, 7.95]	SALT, 1991 10 676 15 684 2.9% 0.67 [0.31, 1.49]		PARIS, 1980 172 1620 52 406 6.3% 0.83 [0.62, 1.11]	
ukCAP, 2008 12 472 15 467 0,7%	0.79 [0.37, 1.67]	SAPAT, 1992 10 1019 19 1026 3.7% 0.53 [0.25, 1.13]		PPP, 2001 62 2226 78 2269 5.6% 0.81 [0.58, 1.13]	-
Subtotal (95% CI) 30394 32249 100.0%	0.99 [0.93, 1.05]	seAFOod, 2018 0 176 1 176 0.3% 0.33 [0.01, 8.13]		SALT, 1991 61 676 69 684 5.6% 0.89 [0.64, 1.24]	
Total events 1944 2477		UK-TIA, 1991 21 1621 23 814 6.0% 0.46 [0.26, 0.82]		SAPAT, 1992 82 1019 106 1026 6.6% 0.78 [0.59, 1.03]	-
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 11.29, df = 11 (P = 0.42); I <sup>2</sup> = 3%		ukCAP, 2008 2 472 3 467 0.6% 0.66 [0.11, 3.93]		seAFOod, 2018 0 324 1 316 0.1% 0.33 [0.01, 7.95]	
Test for overall effect: Z = 0.45 (P = 0.65)		Subtotal (95% CI) 33416 31501 100.0% 1.08 [0.96, 1.22]	*	UK-TIA, 1991 221 1621 122 814 8.2% 0.91 [0.74, 1.12]	*
		Total events 563 499		ukCAP, 2008 12 472 11 467 1.5% 1.08 [0.48, 2.42]	
2.4.2 5-10years		Heterogeneity: Chi <sup>2</sup> = 25.41, df = 16 (P = 0.06); I <sup>2</sup> = 37%		Subtotal (95% CI) 36741 34270 100.0% 0.97 [0.88, 1.08]	•
AAA, 2010 166 1675 194 1675 16.1%	0.86 (0.70, 1.04)	Test for overall effect: Z = 1.28 (P = 0.20)		Total events 2432 2154	
ARRIVE, 2018 276 6270 236 6276 18.0%	1.17 [0.99, 1.39]			Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 45.52, df = 18 (P = 0.0003); I <sup>2</sup> = 60%	
ASCEND, 2018 897 7740 887 7740 24.7%	1.01 [0.93, 1.10]	2.5.2 5-10 years		Test for overall effect: Z = 0.48 (P = 0.63)	
BDS, 1988 194 3429 104 1710 13,7%	0.93 [0.74, 1.17]	AAA, 2010 78 1675 90 1675 10.0% 0.87 [0.64, 1.16]			
JPPP, 2017 332 7297 271 7304 19.0%	1.23 [1.05, 1.43]	ASCEND, 2018 309 7740 315 7740 35.0% 0.98 [0.84, 1.14]	*	2.6.2 5-10 years	
POPADAD, 2008 53 638 68 638 8.5%	0.78 [0.55, 1.10]	BDS, 1988 75 3429 46 1710 6.8% 0.81 [0.57, 1.17]		AAA, 2010 176 1675 186 1675 9.7% 0.95 [0.78, 1.15]	*
Subtotal (95% CI) 27049 25343 100.0%	1.01 [0.90, 1.14]	POPADAD, 2008 25 638 31 638 3.4% 0.81 [0.48, 1.35]		ARRIVE, 2018 160 6270 161 6276 7.9% 0.99 [0.80, 1.23]	+
Total events 1918 1760		TPT, 1998 87 2545 104 2540 11.6% 0.83 [0.63, 1.10]		ASCEND, 2018 748 7740 792 7740 40.7% 0.94 [0.86, 1.04]	
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 13.83, df = 5 (P = 0.02); I <sup>2</sup> = 64%		WHS, 2005 284 19934 299 19942 33.2% 0.95 [0.81, 1.12]	+	BDS. 1988 270 3429 151 1710 10.1% 0.89 [0.74, 1.08]	-
Test for overall effect: Z = 0.23 (P = 0.82)		Subtotal (95% Cl) 35961 34245 100.0% 0.92 [0.84, 1.01]	•	JPPP, 2017 303 7297 308 7304 15.2% 0.98 [0.84, 1.15]	+
		Total events 858 885		POPADAD, 2008 94 638 101 638 5.5% 0.93 [0.72, 1.21]	+
2.4.3 > 10years		Heterogeneity: Chi <sup>z</sup> = 2.13, df = 5 (P = 0.83); l <sup>2</sup> = 0%		TPT, 1998 216 2545 205 2540 10.9% 1.05 [0.88, 1.26]	t
JPAD, 2018 149 1259 169 1277 9.5%	0.89 [0.73, 1.10]	Test for overall effect: $Z = 1.65$ (P = 0.10)		Subtotal (95% CI) 29594 27883 100.0% 0.96 [0.90, 1.02]	1
PHS, 1998 173 11037 168 11034 9.1%	1.03 [0.83, 1.27]	Test for overall effect. $Z = 1.05 (r = 0.10)$		Total events 1967 1904	
WHS, 2005 1438 19934 1427 19942 81.3%	1.01 [0.94, 1.08]	2.5.3 > 10 years		Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.93, df = 6 (P = 0.93); l <sup>2</sup> = 0%	
Subtotal (95% Cl) 32230 32253 100.0%	1.00 [0.94, 1.06]			Test for overall effect: Z = 1.34 (P = 0.18)	
Total events 1760 1764		JPAD, 2018 63 1259 60 1277 14.0% 1.07 [0.75, 1.50] PHS, 1998 79 11037 68 11034 15.9% 1.16 [0.84, 1.60]			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.25, df = 2 (P = 0.53);   <sup>2</sup> = 0%				2.6.3 > 10 years	
Test for overall effect: Z = 0.04 (P = 0.96)		WHS, 2005 284 19934 299 19942 70.1% 0.95 [0.81, 1.12] Subtotal (95% Cl) 32230 32253 100.0% 1.00 [0.88, 1.14]		PHS, 1998 217 11037 227 11034 26.0% 0.96 [0.79, 1.15]	<u>±</u>
·····,				WHS, 2005 609 19934 642 19942 74.0% 0.95 [0.85, 1.06]	
		Total events 426 427		Subtotal (95% Cl) 30971 30976 100.0% 0.95 [0.87, 1.04]	4
	0.01 0.1 1 10 10			Total events 826 869	
	Favours [experimental] Favours [control]	Test for overall effect: Z = 0.00 (P = 1.00)		Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.00, df = 1 (P = 0.95); l <sup>2</sup> = 0%	
				Test for overall effect: Z = 1.06 (P = 0.29)	
		0.01	0.1 1 10 100		
			vours [experimental] Favours [control]		0.02 0.1 1 10 50
					Favours [experimental] Favours [control]
Α		в		c	· exercise feedboundering in a second from real
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**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

 $(\leq 100 \text{ mg/day})$  use for more than five years.

	Experim		Cont			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.7.1 total cancer Inci							
AAA, 2010	166	1675	194	1675	11.4%	0.86 [0.70, 1.04]	
ARRIVE, 2018	276	6270	236	6276	13.3%	1.17 [0.99, 1.39]	
ASCEND, 2018	897	7740	887	7740	21.6%	1.01 [0.93, 1.10]	
JPAD, 2008	149	1259	169	1277	10.7%	0.89 [0.73, 1.10]	
JPPP, 2017	332	7297	271	7304	14.4%	1.23 [1.05, 1.43]	
POPADAD, 2008	53	638	68	638	5.2%	0.78 [0.55, 1.10]	
WHS, 2005	1438	19934	1427	19942	23.3%	1.01 [0.94, 1.08]	T
Subtotal (95% CI)		44813		44852	100.0%	1.01 [0.93, 1.10]	<b>—</b>
Total events	3311		3252				
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup>	= 14.96,	df = 6 (P	= 0.02)	$ ^2 = 60\%$		
Test for overall effect:	Z = 0.27 (F	P = 0.78)	1				
2.7.2 total cancer mo	rtality						
AAA, 2010	78	1675	90	1675	8.9%	0.87 [0.64, 1.16]	
ASCEND, 2018	309	7740	315	7740	33.0%	0.98 [0.84, 1.14]	
JPAD, 2008	15	1262	19	1277	1.7%	0.80 [0.41, 1.57]	
JPPP, 2017	134	7297	125	7304	13.4%	1.07 [0.84, 1.37]	
POPADAD, 2008	25	638	31	638	2.9%	0.81 [0.48, 1.35]	
TPT, 1998	87	2545	104	2540	10.0%	0.83 [0.63, 1.10]	
WHS, 2005	284	19934		19942	30.0%	0.95 [0.81, 1.12]	
Subtotal (95% CI)	204	41091	200		100.0%	0.95 [0.87, 1.04]	•
Total events	932	41001	983		1001070		
Heterogeneity: Tau <sup>2</sup> =		= 2.98		= 0.81).	$l^2 = 0\%$		
Test for overall effect:				0.01),	1 070		
	2 - 1.10 (	- 0.24	/				
2.7.3 all-cause morta	lity						
AAA, 2010	176	1675	186	1675	7.9%	0.95 [0.78, 1.15]	
<b>ARRIVE</b> , 2018	160	6270	161	6276	6.4%	0.99 [0.80, 1.23]	
ASCEND, 2018	748	7740	792	7740	33.3%	0.94 [0.86, 1.04]	
JPAD, 2008	34	1262	38	1277	1.4%	0.91 [0.57, 1.43]	
JPPP, 2017	303	7297	308	7304	12.4%	0.98 [0.84, 1.15]	
POPADAD, 2008	94	638	101	638	4.5%	0.93 [0.72, 1.21]	
TPT, 1998	216	2545	205	2540	8.9%	1.05 [0.88, 1.26]	
WHS, 2005	609	19934	642	19942	25.1%	0.95 [0.85, 1.06]	
Subtotal (95% CI)		47361		47392	100.0%	0.96 [0.91, 1.02]	•
Total events	2340		2433				
Heterogeneity: Tau <sup>2</sup> =				= 0.98);	$ ^2 = 0\%$		
Test for overall effect:	Z = 1.40 (	P = 0.16	)				
							0.5 0.7 1 1.5 2
			ar naar tar		3). I <sup>2</sup> = 0%		Favours [experimental] Favours [control]

**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.

$\frac{1}{2}  table provided in the constraint of the constraint of$	y or Studproup Events Total Fonds Total Weight M-H. Eized, 25% Cl. M-H. Fixed, 35% Cl. Healthy population ,2010 176 1675 186 1675 10.6% 0.95 [0.76, 1.15] REE, 2018 568 9525 494 9589 28.2% 1.14 [1.01, 1.28]
Cite: 2.01     Other Distance     Cite: 2.01     Cit	, 2010 176 1675 186 1675 10.6% 0.95 [0.78, 1.15]
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The result disket $x_{2} = 0.5 (1)^{-0} = 0.50$ . The result is the result of the result is the result of the result is the resu	
2.3.2 Patients with debutes methods   2.3.2 Patients with debutes methods   2.3.2 Patients with debutes methods   7.5.5 Patients with debute	
$ \begin{array}{c} 2 \text{Particular with Gubdess mellitus} \\ \text{SPD}, 2 \text{Strip} & \text{Figs} & \text{Figs}$	rogeneity: Chi <sup>2</sup> = 7.38, df = 4 (P = 0.12); l <sup>2</sup> = 46% for overall effect: Z = 0.12 (P = 0.90)
Carbon state   approx 17740   887   7740   8195   101   1033, 1:01   approx 101   approx 10	for overall effect: Z = 0.12 (P = 0.90)
Display     Tell	2 Patients with diabetes mellitus
$\frac{1}{2} (2, 0, 0) = 53 \ 638 \ 66 \ 638 \ 11.0 \ 50 \ 256 \ 10.0 \ 51 \ 10.0 \ 52.0 \ 50 \ 10.0 \ 11.0 \ 50 \ 10.0 \ 11.0 \ 50 \ 11.0 \ $	END 2018 748 7740 792 7740 60.9% 0.94 [0.86, 1.04]
bill (disk) (i)     9637     9657     9602	IAD, 1989 3 318 3 157 0.3% 0.49 [0.10, 2.42]
idencess   1009   1124   1124   1124     percendents   1009   1124   235   153   1	RS, 1992 340 1856 366 1855 28.1% 0.93 [0.81, 1.06]
componentify: The "= 0.00; Chit" = 2.89; cft = 2 (P = 0.23); P = 33%;     Subleal (95%; Ch)     1184     1167     0.00; Chit" = 1.00; Chit" = 0.05; P = 0.05;     Subleal (95%; Ch)     1184     1167     0.00; Chit" = 1.00; Chit" = 0.05; P = 0.05;     Subleal (95%; Ch)     1184     1167     0.00; Chit" = 1.00; Ch	0,2008 34 1259 38 1277 2.9% 0.91[0.58,143]
Tell owardie diffect Z = 0.81 (P = 0.42)   Total avoards   366   379   Such     9 Participants with CVD or at increased risk of CVD   Total avoards   366   379   Such     5, 1960   50   2207   7.49   10.607, 1.731   Here   Such   Total avoards   366   379   Total avoards   366   779   771   456   770   471   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167   371   167	ADAD 2008 94 638 101 638 7.8% 0.93[0.72, 1.21]
Participants with VVD or at increased risk of CVD   Applicipants with VVD or at increased risk of CVD   Total Participants with VDD or at increased risk of CVD     A point participants with VDD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   AAA, 2010   78   165   90   1675   164   1675   164   177   164   177   164   177   164   177   164   177   164   176   166   177   164   176   166   177   164   176   166   177   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675   164   1675	total (95% Cl) 11811 11667 100.0% 0.94 [0.87, 1.01]
3 Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD     5, 1980   30   2257   4.3   2257   7.3%   1.16 (0.77, 1.73)   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with CVD or at increased risk of CVD   Participants with Partin Partins with Participants with Participants with Par	l events 1219 1300
1, 2010   168   1075   194   1075   194   1075   167, 194   1075   167, 194   1075   167, 194   1075   167, 194   207, 71, 73   1.18   0.17, 173   0.48   0.277   0.276   16.8, 177   0.98   0.276   1.17   0.98   0.277   0.27   0.07   0.59   0.07   0.59   0.07   0.59   0.07   0.44   1.44   0.44   0.28   0.99   0.97   0.44   1.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.44   0.44   0.97   0.97   0.44   0.44   0.97   0.44   1.44   0.44   0.97   0.44   1.44   0.45   0.45   0.07   0.44   1.44   0.45   0.45   0.45   0.45   0.45   0.45   0.45   <	progeneity: Chi <sup>2</sup> = 0.69, df = 4 (P = 0.95); l <sup>2</sup> = 0%
5, 1680   50   2287   43   2287   7.3%   1.16 [0.77, 17.3]   2.8.3 Participants with C/OD or at Increased field C/OD     5%2, 1596   32   1646   28   1649   5.2%   1.14 [0.59, 1.89]   0.87 [6.27, 17.8]   COD or at Increased field C/OD   0.84 [0.27, 17.8]   AAA, 2010   78   377 [1   0.4%   0.34 [0.04, 3.25]   AAA, AMA     7, 1930   1064   12   78 [0.26, 1.16]   0.87 [0.44, 1.14]   AAA, AMA     7, 1010   1009   19   1020   2.5%   0.64 [0.25, 1.16]   CDPA, 1193   1.646   5.6%   0.78 [0.44, 1.24]   AAA, AMA     10 and 183% CDV or at Increased field CVD   1.466   5.6%   0.78 [0.44, 1.44]   AAA   AAA     10 and 183% CDV or at Increased field CVD   1.466   5.6%   0.78 [0.44, 1.44]   AAA     10 and 183% CDV or at Increased field CVD   1.466   5.6%   0.78 [0.44, 1.44]   AAA     10 and 183% CDV or at Increased field CVD   1.66   1.6%   1.09 [0.8, 1.50]   D.04   D.07 [0.41, 1.44]   AAA     10 and 183% CDV or at Increased field CVD   1.66   1.6%   1.6%   1.160 [0.78, 1.54]   D.01	is gravitational to the state $(1 - 0.08)$ is the state $(1 - 0.08)$ is the state $(1 - 0.08)$
2: 2: 0 ads   2: 2: 0 ads   2: 2: 0 ads   2: 2: 0 ads   2: 0 ads   2: 0 ads   2: 0 ads   0: 0 ads <td></td>	
Tiggs   294   339   311   9391   19.5%   0.94 (p31, 1.10]   AMA     P:2017   322   727   7304   10.4%   12.51 (p5, 1.43)   AMA     P:2017   322   729   10.404   12.23 (p38)   10.8 (p0.78)   0.78 (p3.4, 176)   AMA     P:2017   332   7297   7304   10.404   12.87 (p38)   10.8 (p3.6)   730 (p3.6, 1.47)   AMA     P:2017   3147   100.4%   1.261 (p2.6, 1.45)   1.461 (p2.8, 1.16)   AMA     P:2017   3147   1102.25%   0.64 (p2.8, 1.13)   PPP.2017   314   727 (p2.4, 1.44)   AMA     P:2017   3147   1102.45   11.46 (p2.8, 1.13)   PPP.2017   314.7 (p3.9)   10.9 (p3.6, 1.40)   PPP.2017   134.7 (p3.9)   10.7 (p3.6, 1.40)   PPP.2017   134.7 (p3.9)   10.9 (p3.6, 1.40)   PPP.2017   134.44   PPP.2017   134.44   PPP.2017   134.44   PPP.201	.3 Participants with CVD or at Increased risk of CVD
T, 1998   294   9399   311   9391   10.95%   0.04   0.04   1.2   3.78   0.78   0.78   0.47   0.78   0.48   1.74   0.78	2010 176 1675 186 1675 8.9% 0.95 [0.78, 1.15]
2 2001 B8 2228 B0 2289 10.9% 1100 [0.1, 1.4c] 2 4001 1286 1226 25% 0.64 [0.25, 1.15] 2 4071 1282 31947 100.0% 1.4c] 2 4071 1282 31947 100.0% 1.4c] 2 4071 1282 31947 100.0% 1.4c] 2 4071 128 1182 4 107 versal effect Z = 0.07 (P = 0.08), P = 0.04), P = 0.023, P = 0.05 2 4 1071 versal effect Z = 0.07 (P = 0.08), P = 0.04), P = 0.023, P = 0.05 2 4 1071 versal effect Z = 0.02 (Ch <sup>2</sup> = 1.48, dt = 7 (P = 0.05), P = 0.05), P = 0.05 2 4 1071 versal effect Z = 0.02, Ch <sup>2</sup> = 0.290 2 4 102 versat 2 2 2 2 7 7 4 2 5 7 2 10.9% 0.03 (0.08, 1.51] 2 5 2 5 2 2 2 2 7 4 5 2 5 2 2 2 2 7 4 5 2 7 6 2 7 7 5 2 7 6 2 7 7 7 2 7 7 7 2 7 7 7 2 7 7 7 2 7 7	S, 1980 245 2267 219 2257 10.4% 1.11 [0.94, 1.32]
PPP, 2017 134 7297 125 7304 197% 107 (0.41, 137) property 126 1162 al events 126 4 1162 property 127 134 7297 125 7304 197% 107 (0.41, 137) property 126 1202 chi = 14.8 (d = 7 (P = 0.04); i = 52% st for overall effect; Z = 0.67 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.67 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.67 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.67 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.02 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.02 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.02 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 0.02 (P = 0.50); i = 0.04; i = 52% st for overall effect; Z = 1.64 (P = 0.10) st for overall effect; Z = 1.54 (P = 0.51); i = 48%; st for overall effect; Z = 1.54 (P = 0.51); i = 0.05;	RIVE. 2018 160 6270 161 6276 7.7% 0.99 [0.80, 1.23]
biblic 1698 C(1)     31792     31987     1084 [0.92, 1.16]     EAF1       al wonts     1246     1182	PA, 1976 44 758 64 771 3.0% 0.70 [0.48, 1.01]
124 works   124   1162	T, 1993 102 404 99 378 4.9% 0.96 [0.76, 1.22]
SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] Horrisonally: Tau" = 0.02; Ch <sup>2</sup> = 14.8, df = 7 (P = 0.04); P = 82% SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.31, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.25, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.25, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.25, 149] PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.25, 0.22) PARI SALT, 1991 10 476 15 694 3.4% 0.67 (0.25, 0.22) PARI Salt or verail effect Z - 154 (P = 0.15) Heterogeneity: Tau" = 0.02; Ch <sup>2</sup> = 14.45, df = 11 (P = 0.21); P = 24% Heterogeneity: Tau" = 0.02; Ch <sup>2</sup> = 14.45, df = 11 (P = 0.21); P = 24% Heterogeneity: Tau" = 0.02; Ch <sup>2</sup> = 1.44, for ancer salf or verail effect Z = 0.219 (-90.47) Heterogeneity: Tau" = 0.00; Ch <sup>2</sup> = 0.15); P = 0.48 Heterogeneity: Tau" = 0.00; Ch <sup>2</sup> = 0.16); P = 0.48; (0.48, 1.81] PARI APPR Subtotal (95% Cl) 1049 1049 1049 1049 1049 0.040, 0.81 (0.40, 1.10] UCAP, 2008 2 472 3 467 76.2% 0.68 (0.12, 2.88] APR PARI Subtotal (95% Cl) 1049 1049 1049 0.040, 0.81 (0.40, 1.10] UCAP, 2008 2 472 3 467 76.2% 0.66 (0.12, 2.88] APR Subtotal (95% Cl) 1049 1049 1049 0.040, 0.81 (0.40, 1.81] Subtotal (95% Cl) 1049 1049 0.040, 0.81 (0.40, 1.81] Subtotal (95% Cl) 1049 1049 0.020; Ch <sup>2</sup> = 0.47; P = 0.42; P = 0.47; P = 0.42; P = 0.46;	PS-2, 1996 367 3299 390 3303 18.6% 0.94 [0.82, 1.08]
at for overall effect: Z = 0.67 (P = 0.50)   SAPAT. 1992   10 1019   19 1026   3.8%   0.53 (0.25, 1.13)   PPR     24 Individuals at increased risk for cancer   PPPS, 2003   28 775   10 1019   19 1026   3.8%   0.48 (0.76, 0.08)   100   PPR     20 CGP, 2006   12 472   15 467   140 (0.26, 0.52)   11 4021   23 814   5.8%   0.48 (0.76, 1.03)   PPR     1 usiontal (9% Cl)   2589   4008   100.0%   1.00 (0.66, 1.54)   100 (0.26, 0.52)   PPR   PPR     1 usiontal (9% Cl)   2589   4008   100.0%   1.00 (0.66, 1.54)   100 (0.26, 0.52)   PPR   PPR     1 usiontal (9% Cl)   2589   4008   100.0%   1.00 (0.66, 1.54)   100 (0.26, 0.52)   PPR   PPR     1 usiontal (9% Cl)   2589   4008   100.0%   107 (0.27)   PPR   2.4 (PP - 0.10)   PPR   PPR     2.94 Individuals at increased risk for cancer   set for overail effect: Z = 1.64 (P = 0.10)   UCCAP, 2008   2 472   3 467   76.2%   0.65 (0.11, 3.33)   OUI (1.1,	r, 1998 284 9399 305 9391 14.5% 0.93 [0.79, 1.09]
All only duals at increased risk for cancer   TPT, 1998   87   2546   104 5%   0.4 0.9%   0.83 (0.53, 1.0)   PARI     Linkividuals at increased risk for cancer   Subtolal (95% Cl)   30869   28907   100.0%   0.88 (0.76, 1.03)   PPR     EDUCE, 2015   288   1368   773   15   4607   2.14%   0.78 (0.26, 0.27)   0.88 (0.76, 1.03)   PPR     Jatobal (95% Cl)   2289   7100.0%   1.00 (0.46, 1.54)   1.00 (0.46, 1.54)   Total ownts   525   550     Hoterogeneity: Tau <sup>1</sup> = 0.02; Ch <sup>1</sup> = 3.33, df = 2 (P = 0.15); H = 48%   attor overall effect; Z = 1.54 (P = 0.10)   Heterogeneity: Tau <sup>1</sup> = 0.02; Ch <sup>2</sup> = 4.45, df = 11 (P = 0.21); H = 24%   Total ownts   525     Stor overall effect; Z = 1.54 (P = 0.15); H = 4.8%   attor overall effect; Z = 1.54 (P = 0.10)   Heterogeneity: Tau <sup>1</sup> = 0.02; Ch <sup>2</sup> = 0.47;   33 (0.01, 8.13)   Z.40   Chi (V = 0.21); H = 24%     Stor overall effect; Z = 1.54 (P = 0.51); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z = 0.24 (P = 0.15); H = 4.8%   attor overall effect; Z	P, 2017 303 7297 308 7304 14.7% 0.98 [0.84, 1.15]
L4 Individuals at increased risk for cancer PPF, 2003 28 74 7 372 18.9% 1.98 (0.84, 0.84) DD(CE, 2016 286 1388 753 3166 58.7% 0.88 (0.78, 0.98) DD(CE, 2016 286 1388 753 3166 58.7% 0.88 (0.78, 0.98) Dotal (9% Ct) 2289 4008 100.0% 1.00 [0.88, 1.54] Lai avents 326 775 terogenely: Tai <sup>2</sup> 0.02; CH <sup>0</sup> + 3.83, df = 2 (P = 0.15); P = 48%, at for overall effect: Z = 1.64 (P = 0.10) Test or overall effect: Z = 1.64 (P = 0.10) L4 (0.9% Ct) 1049 100.0% 0.81 [0.60, 1.10] Lai events 70 85 terogenely: Tai <sup>2</sup> 0.02; CH <sup>0</sup> = 4.64; P = 0.51; P = 0%, at for overall effect: Z = 1.34 (P = 0.51); P = 0%, at for overall effect: Z = 1.34 (P = 0.51); P = 0%, at for overall effect: Z = 1.34 (P = 0.51); P = 0%, at for overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 1.34 (P = 0.51); P = 0%, the overall effect: Z = 0.32 (P = 0.47); P = 0%, the overall effect: Z = 0.32 (P = 0.51); P = 0%, the overall effect: Z = 0.32 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0.51); P = 0%, the overall effect: Z = 0.34 (P = 0	RIS, 1980 172 1620 52 406 4.0% 0.83 [0.62, 1.11]
prps   203   28   749   7   372   18.9%, 1.96 [0.8, 4.51]     prps   200/CE, 2015   266   138   575   316 (0.78, 4.51)   Total avonts   525   550     CAP, 2020   12   472   15   467   21.4%, 0.79 [0.37, 187]   Total avonts   525   550     Lai oversal   368   775   383, d1 = 2 (P = 0.15); P = 48%, d1 = 0.0%, 1.00 [0.46, 1.54]   Total avonts   525   550     Lai oversal   164 coresal   366 (C = 11, P = 0.21); P = 24%, d1 = 0.0%   176   1   176   23.9%, 0.33 [0.01, 8.13]   AFT   Total avonts   24.40   78.40   34.67   78.2%, 0.33 [0.01, 8.13]   AFT   Total avonts   24.64 (P = 0.10)   Heterogeneity: Tau" = 0.00; ChiP = 0.13; d= 1 (P = 0.71); P = 0%; d6 (0.11, 3.83]   AFT	2,2001 62 2226 78 2269 3.7% 0.81 [0.58, 1.13]
DuCE_2016     286     138.3     75.3     3169     59.7%     0.88 [0.78, 0.96]     Total ovents     525     550     Subto       biobal (95% C)     2589     4.008     100.0%     1.00 [0.86, 1.54]     Heige     Heige     1.00 [0.86, 1.54]     Total ovents     525     550     Subto     1.00 [0.86, 1.54]     Total ovents     1.00 [0.86, 1.10]     Total ovents     2.34 Individuals at increased risk for cancer     2.34 Individuals at increased risk for concer     2.34 Indiv	, 1998 216 2545 205 2540 9.8% 1.05 [0.88, 1.26]
CAP_2003   12   472   15   467   21.4%   0.79 [0.37, 1.87]     Inbiand (9%, C)   2.89   4008   10.00 [0.48, 1.54]   1.00 [0.48, 1.54]   Test for overall effect. Z = 16.4 (P = 0.01)     Ist or overall effect. Z = 0.02 (P = 0.99)   3.5 Patients with peripheral arterial disease or venous thromboembolism.   176   1.16   176   2.19, Midfuldust 8 intercessed risk for cancer   2.40     Subtotal (9%, C1)   1049   100.9%   0.37 [0.55, 1.10]   116   117   2.3 467 (76.2%)   0.66 [0.11, 3.33]   467   2.40     PPRE, 2012   17   411   16   411   2.10, three openeity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, three openeity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.47)   2.40   43 100.0%   0.56 [0.12, 2.86]   Mick     PPRE, 2012   17   411   16   411   2.9, Patients with peripheral arterial disease or venous thromboembolism.   56 (0.12, 2.86]   Mick     Total events   70   86   56 (0.6, 1.2, 2.86]   1.00 (0.43, 5.28]   1.00 (0.43, 5.28]   1.00 (0.48, 1.35)   1.00 (0.48, 1.36)   1.00 (0.48, 1.36)   1.00 (0.48, 1.45)   1.00 (0.48, 1.45)   CLIPS, 2007   1   91   90   2.2% 7 (0.12, 7.189)   2.10, three openein	total (95% Cl) 37760 36570 100.0% 0.96 [0.91, 1.02]
bibble display Chi     2589     4008     10.00 (0.86, 1.54)     Test for overall effect: Z = 1.64 (P = 0.10)     Hele       late works     266     775     176     2.8.4 Individuals at increased risk for cancer     Test for overall effect: Z = 1.64 (P = 0.10)     Test for overall effect: Z = 1.64 (P = 0.10)     Test for overall effect: Z = 1.64 (P = 0.10)     Hele       staf for overall effect: Z = 0.02 (P = 0.99)     3.8.3 (ff = 2 (P = 0.10)     Subtotal (85% Ch)     1.16 2.3.8%     0.33 [0.01, 8.13]     AFPI     Aspin Line     AFPI     Subtotal (85% Ch)     0.46 (7.6, 2.08)     2.472     3.467     76.2%     0.65 [0.11, 3.33]     AFPI     Subtotal (85% Ch)     0.46 (7.6, 2.08)     2.4     0.65 [0.12, 2.68]     Subtotal (85% Ch)     1.16 (2.0.02) <td>al events 2131 2067</td>	al events 2131 2067
all avoints     2.8.4 Individuals all increased rekk for cancer     2.8.4 Individuals all increased rekk for cancer     2.8.4 Individuals all increased rekk for cancer       2.8.4 Individuals all increased rekk for cancer     2.8.4 Individuals all increased rekk for cancer     3.8.4 for 2, 20 g = 0.99)     3.8.3 (d = 2, 1P = 0.95); P = 4.8%;     4.87     7.6.2%;     0.66 [0, 11, 3.83];     AFPF;       1.8 tor overall effect: Z = 0.02; (P = 0.99)     1.16 + 21.8 %;     0.56 [0, 12, 2.86];     AFP;     AFP; <td< td=""><td>erogeneity: Chi<sup>2</sup> = 9.04, df = 10 (P = 0.53); l<sup>2</sup> = 0%</td></td<>	erogeneity: Chi <sup>2</sup> = 9.04, df = 10 (P = 0.53); l <sup>2</sup> = 0%
set or overall effect. Z = 0.02 (P = 0.05), P = 0.05, P	t for overall effect: Z = 1.23 (P = 0.22)
at or overall effect: 2 = 0.3 (P = 0.99)   uCCP, 2009   2 472   3 467   75,2%   0.68 [0.11,3.03]   AFPI     Subbotal (95% Cl)   13 411   21.7%   0.94 [0.40, 1.81]   Total events   2 472   3 467   75,2%   0.68 [0.11,3.03]   UCCP, 2009   2 472   3 467   75,2%   0.68 [0.11,3.03]   UCCP, 2009   0.56 [0.12,2.66]	
1.5 Patients with partpharal arterial disease or venous thromboembolism   Subtrait (95% Cl)   648   643   100.0%   0.56 (0.12, 2.66)   Subtrait (95% Cl)   0.46 (0.49, 181)     PIRE, 2012   17   411   16   411   21,7%   0.96 (0.42, 2.66)   Subtrait (95% Cl)   0.46 (0.49, 181)   Total events   2   4   Subtrait (95% Cl)   104.04   1.05 (0.12, 2.66)   Subtrait (95% Cl)   104.04   1.01 (0.1 (0.1 (0.1 (0.1 (0.41)))   Total events   2   4   1.01 (0.41, 1.42)   Total events   2   4   1.01 (0.41, 1.42)   Total events   1.01 (0.41, 1.42)   Total events   1.01 (0.41, 1.42)   Total events   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   Total events   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   1.01 (0.41, 1.42)   2.05   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42)   2.01 (0.41, 1.42) <td< td=""><td>).4 Individuals at increased risk for cancer</td></td<>	).4 Individuals at increased risk for cancer
PipeE_2012 17 411 18 411 21.7% 0.49 (0.49, 18.1] Total events 2 4 Subt   PacADA 2006 55 65.3 67.83% 67.36 (0.51) Feast Feast 70.00 (Chi = 0.26, di = 1 (P = 0.71); P = 0% Total events Total events 2 4 Subt   a levents 70 86 68.05 (Chi = 0.26, di = 1 (P = 0.61); P = 0% 0.81 [0.60, 1.10] Test for overail effect: Z = 0.73 (P = 0.47)	PPS, 2003 7 749 3 372 26.6% 1.16 [0.30, 4.46]
PADAD, 2008     53     638     68     538     76.3%     0.78 [0.55, 1.10]     Heterageneity: Tau" = 0.00; ChF = 0.13, df = 1 (P = 0.71); P = 0%     Total       stotal (9% Cl)     1049     1049 (100.0%     0.85 [0.60, 1.10]     Test for overall effect: Z = 0.73 (P = 0.13, df = 1 (P = 0.71); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Tau" = 0.00; ChF = 0.26, df = 1 (P = 0.51); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Tau" = 0.00; ChF = 0.26, df = 1 (P = 0.51); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Tau" = 0.00; ChF = 0.26, df = 1 (P = 0.51); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Tau" = 0.00; ChF = 0.26, df = 1 (P = 0.51); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Tau" = 0.00; ChF = 0.26, df = 1 (P = 0.51); P = 0%     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Heterageneity: Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect: Z = 0.73 (P = 0.47)     Test for overall effect	AP, 2008 12 472 11 467 73.4% 1.08 [0.48, 2.42]
bitchail (95% Ct)     1043     105     1043     1043     105	
tale events     70     85     2.9.5 Patients with peripheral arterial disease or venue thromboembolism     Test       derogenely:     71.34 (P = 0.26), df = 1 (P = 0.51); P = 0%     2.9.5 Patients with peripheral arterial disease or venue thromboembolism     2.10       ASPIRE:     2012     6     411     4     411     1.41 (%     1.50 [0.42, 5.28]     2.10       0.01     0.1     1     10     10     POPADAD.2008     2.83 (6.38 8.26 %)     0.81 (0.04, 1.35)     CLIPS.     CLIPS.     2.9.7 [0.12, 71.89]     ASPI     ASPI     ASPI     CLIPS.     2.9.7 [0.12, 71.89]     ASPI     ASPI     CLIPS.     ASPI     CLIPS.     2.9.7 [0.12, 71.89]     ASPI     ASPI     CLIPS.     ASPI     CLIPS.     2.9.7 [0.12, 71.89]     ASPI     CLIPS.     ASPI     CLIPS.     Subtrating %% (C)     1140     1139     100.8% (0.85, 1.45]     CLIPS.     Subtrating %% (C)     Total events     3.2     35     Total     Total events     Subtrating %% (C)     Total events     3.2     3.5     Total events     Total events     Total events     Total events     3.2     3.5     <	
errogeney; Tayl = 0.00; ChP = 0.26, df = 1 (P = 0.61); P = 0%;     2.9.5 Patients with peripheral aterial disease or venous thrombosoliam     2.10       it for overall effect; Z = 1.34 (P = 0.16); P = 0%;     CLIPE; 2012     6     41     11.11 1.4%     1.50 (0.43, 5.28)     2.10       0.01     0.1     100     POPADAD, 2008     2.68 (0.43, 5.28)     CLIPE; 2012     CLIPE; 2017     1     91     0     90     2.2%     2.97 (0.12, 7.189)     CLIPE; 2017     1     110     POPADAD; 2018     2.97 (0.12, 7.189)     CLIPE; 2017     1     110     10.048, 1.35     CLIPE; 2017     1     110     POPADAD; 2018     2.97 (0.12, 7.189)     CLIPE; 2017     CLIPE; 2017     1     110     POPADAD; 2018     2.97 (0.12, 7.189)     CLIPE; 2017     Total with eripheral aterial disease or venous thrombosoliam     CLIPE; 2017     1     110     POPADAD; 2018     2.97 (0.12, 7.189)     CLIPE; 2017     CLIPE; 2017     Total with eripheral aterial disease or venous thrombosoliam     CLIPE; 2017     1     110     10.00, %     0.91 (0.46, 1.45)     Subtatal (9%, CI)     Total with eripheral aterial disease or venous thrombosoliam     CLIPE; 2017     Total with eripheral aterial disease or venous thrombosoliam </td <td>erogeneity: Chi<sup>2</sup> = 0.01, df = 1 (P = 0.93); i<sup>2</sup> = 0% t for overall effect: Z = 0.27 (P = 0.79)</td>	erogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); i <sup>2</sup> = 0% t for overall effect: Z = 0.27 (P = 0.79)
Aprile: 2 1.34 (P = 0.15), P = 0% Aprile: 212 6 411 4 411 14.1% 150 [0.43, 5.28] 2.10, CLIPS, 2007 1 91 0 90 2.2% 2.97 [0.12, 71.89] ASP CLIPS, 2007 1 91 0 90 2.2% 2.97 [0.12, 71.89] CLIPS, 2007 1 91 0 90 2.2% 2.97 [0.14, 15] CLIPS, 2007 1 91 0 90 2.2\% 2.97 [0.14, 15] CLIPS, 2007 1 91 0 90 2.2\% 2.97 [0.14, 15] CLIPS, 2007 1 91 0 90 2.2\% 2.97 [0.14, 15] CLIPS, 2007 1 91 0 90 2.2\% 2.97 [0.14, 15] CLIPS, 2007 1 91 0 91 0 91 0 91 0 91 0 91 0 91 0	Tor overall effect: Z = 0.27 (P = 0.79)
CLIPS.2007     1     91     0     90     2.2%     2.97 [0.12, 71.89]     ASP       0.01     0.1     1     10     10     POPADAD,2008     25     638     83.8%     0.81 [0.48, 1.35]     CLIP       1 for subbroub differences: ChiP = 3.20. df = 4 (P = 0.53), IP = 0%     Favours [control]     Total events     32     35     Total	0.5 Patients with peripheral arterial disease or venous thromboembolism
If or subbroub differences: Chi <sup>p</sup> = 3.20. df = 4 (P = 0.53), I <sup>p</sup> = 0%     Point I     1     0     1     0     1     0     1     0     1     0     1     0     3     0.81 (0.48, 1.95)     CLIP     3     3     0.81 (0.48, 1.95)     CLIP     3     3     0.81 (0.48, 1.95)     CLIP     3     3     0.91 (0.46, 1.45)     5     3     3     1     0.91 (0.56, 1.45)     5     3	PIRE, 2012 16 411 18 411 81.7% 0.89 [0.46, 1.72]
0.01 0.1 1 10 <sup>10</sup> Subtotal (95% Cl) 1140 1139 100.0% 0.91 [0.56, 1.45] t for subarous differences: Ch <sup>ie</sup> = 3.20. df = 4 (P = 0.53), I <sup>e</sup> = 0% Favours [control] Total events 32 35 Total	PRC, 2012 10 411 18 411 81.7% 0.88 [0.46, 1.72]
t for subarous differences: Ch <sup>a</sup> = 3.20. df = 4 (P = 0.53), l <sup>a</sup> = 0% Favours [experimental] Favours [control] Total events 32 35 Total	atotal (95% Cl) 596 592 100.0% 1.04 [0.59, 1.85]
	al events 23 22
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.35, df = 2 (P = 0.51); l <sup>2</sup> = 0%	erogeneity: Chi <sup>2</sup> = 0.87, df = 1 (P = 0.35); l <sup>2</sup> = 0%
	t for overall effect: Z = 0.13 (P = 0.89)
1621	101 044101 41400 E = 0.10 (t = 0.03)
termination of the second	· · · · · · · · · · · · · · · · · · ·
	0.01 0.1 1 10
Favours [experimental] Favours [control]	Favours (experimental) Favours (contr
A B	c

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,

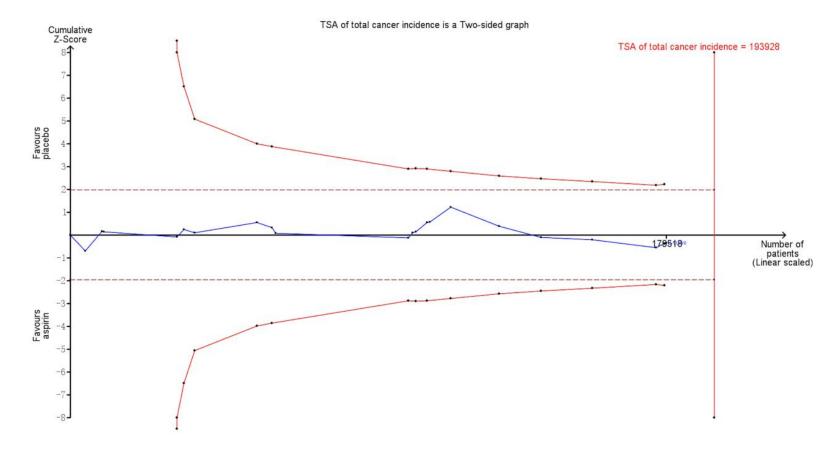
or > 300 mg daily) significantly increased the risk of major bleeding and total bleeding events. A) Major bleeding, B) total bleeding events.

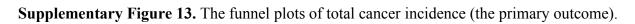
	Experim		Cont			Risk Ratio	Risk Ratio			Experim		Contro			Risk Ratio	Risk R	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed. 95% C	M-H. Fixed. 95% Cl		Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H. Rando	m. 95% Cl
$3.3.1 \leq 100$ mg daily									$3.4.1 \leq 100$ mg daily								
AAA, 2010	34	1675		1675		1.70 [0.98, 2.94]			ARRIVE, 2018	69	6270		6276	10.3%	1.73 [1.17, 2.54]		-
AFPPS, 2003	8	377	5	372	0.6%	1.58 [0.52, 4.78]		-	ASPIRE, 2012	14	411	8	411	3.0%	1.75 [0.74, 4.13]	T	
<b>ARRIVE</b> , 2018	4	6270	2		0.2%	2.00 [0.37, 10.93]			CLIPS, 2007	4	185	0	181	0.3%	8.81 [0.48, 162.40]		
<b>ASCEND</b> , 2018	314	7740	245	7740		1.28 [1.09, 1.51]			ESPS-2, 1996	135	1649		1649	14.8%	1.82 [1.39, 2.40]	1	-
<b>ASPIRE</b> , 2012	8	411	6	411	0.7%	1.33 [0.47, 3.81]			HOT, 1998	292	9399		9391	19.4%	1.77 [1.46, 2.14]		*
ASPREE, 2018	361	9525	265			1.37 [1.17, 1.60]	-		JPAD, 2017	80	1262		1277	13.0%	1.21 [0.88, 1.66]	T	
ESPS-2, 1996	20	1649	7	1649	0.8%	2.86 [1.21, 6.74]			POPADAD, 2008	28	638	31	638	7.3%	0.90 [0.55, 1.49]		
HOT, 1998	136	9399	78	9391	8.9%	1.74 [1.32, 2.30]			PPP, 2001	25	2226		2269	3.8%	2.83 [1.32, 6.05]		
JPAD, 2008	18	1262	12	1277	1.4%	1.52 [0.73, 3.14]			SALT, 1991	49	676	22	684	7.5%	2.25 [1.38, 3.68]		-
JPPP, 2017	104	7220	70	7244	8.0%	1.49 [1.10, 2.01]			SAPAT, 1992	27	1009		1026	5.4%	1.72 [0.93, 3.17]	Ē	
POPADAD, 2008	28	638	31	638	3.5%	0.90 [0.55, 1.49]			WHS, 2005	127			9942	15.2%	1.40 [1.07, 1.83]	=	
PPP, 2001	25	2226	9	2269	1.0%	2.83 [1.32, 6.05]			Subtotal (95% CI)		43659		3744	100.0%	1.61 [1.37, 1.89]		•
SALT, 1991	40	676	18		2.0%	2.25 [1.30, 3.88]			Total events	850		523					
SAPAT, 1992	20	1009	13	1026	1.5%	1.56 [0.78, 3.13]			Heterogeneity: Tau <sup>2</sup> =				= 0.08)	); l <sup>2</sup> = 40%			
TPT, 1998	9	1268		1272		2.26 [0.70, 7.31]			Test for overall effect:	Z = 5.88 (	P < 0.000	01)					
WHS, 2005	127	19934		19942		1.40 [1.07, 1.83]									*		
Subtotal (95% CI)		71279	01		100.0%	1.44 [1.32, 1.57]	•		3.4.2 100-300mg daily	У							
Total events	1256		876						EAFT, 1993	35		25	378	17.5%	1.31 [0.80, 2.15]	1	
Heterogeneity: Chi <sup>2</sup> =		15 (P =		= 11%					PHS, 1989	2979		2248 1		58.1%	1.32 [1.26, 1.39]		
Test for overall effect:				1170					UK-TIA, 1991	60	806	28	814	20.6%	2.16 [1.40, 3.35]		
rest for overall effect.	2 - 0.50 (1	- 0.000	<i>(</i> )						ukCAP, 2008	5	472	5	467	3.7%	0.99 [0.29, 3.40]		
3.3.2 100-300mg dail	v								Subtotal (95% CI)		12719	1	2693	100.0%	1.45 [1.13, 1.85]	1	•
EAFT, 1993	y 6	404	4	378	12.1%	1.40 [0.40, 4.93]		_	Total events	3079		2306				1	
PHS, 1989		11037			87.9%	1.60 [1.01, 2.52]			Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>2</sup>	<sup>e</sup> = 5.00, d	f = 3 (P = )	0.17); F	² = 40%			
Subtotal (95% CI)	40	11441	30		100.0%	1.58 [1.03, 2.42]			Test for overall effect:	Z = 2.94 (	P = 0.003	)					
	54	11441	04	11412	100.0 %	1.50 [1.05, 2.42]											
Total events	54		34	20/					3.4.3 > 300mg daily								
Heterogeneity: Chi <sup>2</sup> =				0%					BDS, 1988	34	3429	13	1710	17.7%	1.30 [0.69, 2.46]	+	
Test for overall effect:	Z = 2.08 (F	<sup>2</sup> = 0.04)							CDPA, 1976	52	727	36	744	21.5%	1.48 [0.98, 2.23]	F	-
0.0.0.000 1.1									DAMAD, 1989	0	318	1	157	2.1%	0.17 [0.01, 4.03]		
3.3.3 > 300mg daily						and a second second			ETDRS, 1992	37	1856	37	1855	20.9%	1.00 [0.64, 1.57]	-+	-
AFPPS, 2003	14	749	5			1.39 [0.50, 3.83			PARIS, 1980	131	1620	8	406	16.5%	4.10 [2.03, 8.31]		
BDS, 1988	14	3429		1710		1.16 [0.45, 3.02			UK-TIA, 1991	77	815	28	814	21.4%	2.75 [1.80, 4.19]		
PHS, 1989	48	11037	30	11034		1.60 [1.01, 2.52			Subtotal (95% CI)		8765	130356	5686	100.0%	1.72 [1.06, 2.78]	4	•
Subtotal (95% CI)		15215		13116	100.0%	1.49 [1.02, 2.18]			Total events	331		123					
Total events	76		41						Heterogeneity: Tau <sup>2</sup> =	0.24: Chi	<sup>2</sup> = 19.76.	df = 5 (P =	0.001	):   <sup>2</sup> = 75%	0		
Heterogeneity: Chi <sup>2</sup> =	0.37, df = 2	2 (P = 0.	83); l² = (	0%					Test for overall effect:			- 13					
Test for overall effect:	Z = 2.06 (F	P = 0.04)	)														
								+ +								0.01 0.1 1	10 100
							0.1 0.2 0.5 1 2	5 10								Favours [experimental]	Favours [control]
					Α		Favours [experimental] Favours [control	n]							В		
					A										D		

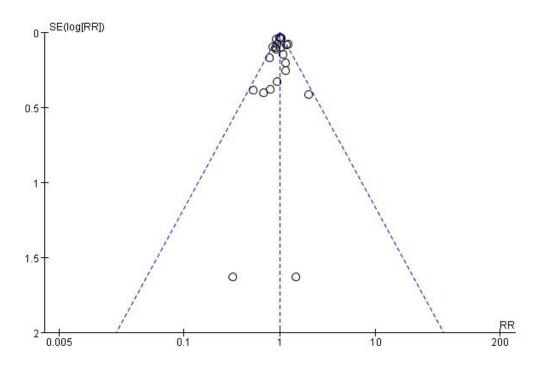
**Supplementary Figure 11.** Subgroup analysis based on follow-up duration showed that the risk of major bleeding and total bleeding events significantly increased with different follow-up durations (1-5 years, 5-10 years, or > 10 years). A) Major bleeding, B) total bleeding events.

and a second second	Experimental	Con			Risk Ratio	Risk Ratio		Experime		Conti			<b>Risk Ratio</b>		Ratio	
	Events Total	Events	Total	Weight	M-H. Fixed. 95% Cl	M-H. Fixed. 95% CI	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	ed. 95% Cl	
3.5.1 1-5years		23	5155333	100000000			3.6.1 1-5 years									
AFPPS, 2003	14 749	5			1.39 [0.50, 3.83]		ASPIRE, 2012	14	411	8	411	1.9%	1.75 [0.74, 4.13]	-		
ASPIRE, 2012	8 411	6		1.1%	1.33 [0.47, 3.81]		CDPA, 1976	52	727	36	744	8.6%	1.48 [0.98, 2.23]			
ASPREE, 2018	361 9525	265		49.9%	1.37 [1.17, 1.60]		CLIPS, 2007	4	185	0	181	0.1%	8.81 [0.48, 162.40]			
EAFT, 1993	4 372	4		0.8%	1.00 [0.25, 3.97]		DAMAD, 1989	0	318	1	157	0.5%	0.17 [0.01, 4.03]			
ESPS-2, 1996	20 1649	7	1649	1.3%	2.86 [1.21, 6.74]		EAFT, 1993	35	404	25	378	6.3%	1.31 [0.80, 2.15]	-		
HOT, 1998	136 9399	78	9391	14.7%	1.74 [1.32, 2.30]		ESPS-2, 1996	135	1649	74	1649	17.9%	1.82 [1.39, 2.40]		-	
JPAD, 2008	18 1262	12	1277	2.3%	1.52 [0.73, 3.14]		ETDRS, 1992	37	1856	37	1855	9.0%	1.00 [0.64, 1.57]		-	
PHS, 1989	48 11037	30	11034	5.7%	1.60 [1.01, 2.52]		HOT, 1998	292	9399	165	9391	40.0%	1.77 [1.46, 2.14]		-	
PPP, 2001	25 2226	9	2269	1.7%	2.83 [1.32, 6.05]		PARIS, 1980	131	1620	8	406	3.1%	4.10 [2.03, 8.31]			
SALT, 1991	20 676	9	684	1.7%	2.25 [1.03, 4.90]		PPP, 2001	25	2226	9	2269	2.2%	2.83 [1.32, 6.05]			
SAPAT, 1992	20 1009	13	1026	2.4%	1.56 [0.78, 3.13]		SALT, 1991	49	676	22	684	5.3%	2.25 [1.38, 3.68]			
WHS, 2005	127 19934	91	19942	17.2%	1.40 [1.07, 1.83]		SAPAT, 1992	27	1009	16		3.8%	1.72 [0.93, 3.17]			
Subtotal (95% CI)	58249	24		100.0%	1.51 [1.35, 1.68]	•	ukCAP, 2008	5	472	5	467	1.2%	0.99 [0.29, 3.40]			
Total events	801	529	1				Subtotal (95% CI)		20952	0		100.0%	1.77 [1.57, 1.99]		•	
Heterogeneity: Chi <sup>2</sup> = 9							Total events	806	20002	406	10010	100.070	in Trior, nool			
Test for overall effect:			070				Heterogeneity: Chi <sup>2</sup> = 2		10 /D - /		440/					
Test for overall effect.	2 = 1.55 (F < 0.000	,01)					Test for overall effect:				- 4170					
3.5.2 5-10years							rest for overall effect:	Z = 9.30 (P	< 0.000	01)						
AAA, 2010	34 1675	20	1675	5.6%	1.70 [0.98, 2.94]		3.6.2 5-10 years									
ARRIVE, 2018	12 6270		6276		0.92 [0.42, 2.02]		ARRIVE, 2018	69	6270	40	6276	1.7%	1.73 [1.17, 2.54]			
ASCEND, 2018	314 7740		7740		1.28 [1.09, 1.51]		BDS, 1988	34	3429		1710					
BDS, 1988	14 3429		5 1710		1.16 [0.45, 3.02]							0.7%	1.30 [0.69, 2.46]			
	104 7220		) 7244		1.49 [1.10, 2.01]		PHS, 1989	2979	11037		11034	96.2%	1.32 [1.26, 1.39]			
JPPP, 2017					2.01 [0.61, 6.65]		POPADAD, 2008	28	638	31	638	1.3%	0.90 [0.55, 1.49]		1	
TPT, 1998	8 1268 27602	4	1272	1.1% 100.0%		•	Subtotal (95% CI)		21374		19658	100.0%	1.33 [1.26, 1.39]		1	
Subtotal (95% CI)		0.50		100.0%	1.34 [1.17, 1.53]		Total events	3110		2332						
Total events	486	358	Second Second				Heterogeneity: Chi <sup>2</sup> =				6%					
Heterogeneity: Chi <sup>2</sup> = 2			0%				Test for overall effect:	Z = 11.69 (	(P < 0.00	001)						
Test for overall effect:	Z = 4.24 (P < 0.00	01)														
							3.6.3 > 10 years								L	
3.5.3 > 10years							JPAD, 2017	80	1259	67		42.2%	1.21 [0.88, 1.66]			
JPAD, 2017	11 1259			11.0%	0.74 [0.34, 1.61]		WHS, 2005	127	19934	91	19942	57.8%	1.40 [1.07, 1.83]			
PHS, 1989	48 11037			22.1%	1.60 [1.01, 2.52]		Subtotal (95% CI)		21193		21219	100.0%	1.32 [1.07, 1.62]		•	
WHS, 2005	127 19934	91	1 19942	67.0%	1.40 [1.07, 1.83]		Total events	207		158						
Subtotal (95% CI)	32230		32253	100.0%	1.37 [1.10, 1.71]	-	Heterogeneity: Chi <sup>2</sup> =	0.45, df = 1	(P = 0.5)	50);   <sup>2</sup> = 0	%					
Total events	186	130	3				Test for overall effect:	Z = 2.65 (F	= 0.008	3)						
Heterogeneity: Chi <sup>2</sup> =	2.85, df = 2 (P = 0.	24); l <sup>2</sup> =	30%													
Test for overall effect:															l	
														0.01 0.1	1 10	100
														Favours [experimental]	Favours [control]	
						0.2 0.5 1 2 5										
						Favours [experimental] Favours [control]										
				А									в			

**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.







Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Othe bias
AAA, 2010 <sup>1</sup>	+	+	+	+	+	+	?
AFPPS, 2003 <sup>2</sup>	+	+	+	+	+	+	?
AMIS, 1980 <sup>3</sup>	+	+	+	+	+	+	?
ARRIVE, 2018 4	+	+	+	+	+	+	?
ASCEND, 2018 <sup>5</sup>	+	+	+	+	+	+	?
ASPIRE, 2012 6	+	+	+	+	+	+	?
ASPREE, 2018 <sup>7</sup>	+	+	+	+	+	+	?
BDS,1988 <sup>8</sup>	+	-	-	+	+	+	?
CDPA, 1980 <sup>9</sup>	+	+	+	+	+	+	?
CLIPS, 2007 10	+	+	+	+	+	+	?
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 31	+	+	+	+	+	+	?
WHS, 2005 <sup>32</sup>	+	+	+	+	+	+	?

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

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

AAA, Aspirin for Asymptomatic AtherosclerosisTrial; 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.

			v			-		Summary of findings					
	Indicators	(Trials)		(	Quality assessmen	it		No. of p	oatients	- Relative risk	Absolute effects		
	Indicators	(Triais)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Aspirin	No apsirin	(95% CI)	Risk difference (95% CI)	Quality	
	Total cancer inc	eidence (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 mo	ortality (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))#	0 more per 1000 (-1 to 1)	⊕⊕⊕⊕ High	
	All-cause mor	tality (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))#	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))#	4 more per 1000 (3 to 5)	⊕⊕⊕⊕ High	
	Total bleeding	events (19)	No serious <sup>b</sup>	Serious <sup>e</sup>	No serious	No serious	Undetected	4123/63519 (6.49%)	2896/60495 (4.79%)	1.52 (1.33 to 1.74)*	17 more per 1000 (15 to 20)	⊕⊕⊕O Moderate	
	Subgroup a	nalyses											
		$\leq$ 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	
	Dose of aspirin	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	
		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)*	13 fewer per 1000 (-17 to -9)	⊕⊕⊕⊕ High	
	Follow-up duration	5-10 years (6)	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	1918/27049 (7.09%)	1706/25343 (6.73%)	1.01 (0.90 to 1.14)*	2 more per 1000 (-3 to 6)	⊕⊕⊕O Moderate	
Total cancer		>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)*	0 fewer per 1000 (-4 to 3)	⊕⊕⊕⊕ High	
incidence		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)*	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)*	2 fewer per 1000 (-11 to 7)	⊕⊕⊕⊕ High	
	Study populations	With CVD or at increased risk of CVD (8)	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	1246/31972 (3.92%)	1182/31847 (3.71%)	1.04 (0.92 to 1.19)*	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)*	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)*	15 fewer per 1000 (-38 to 7)	⊕⊕⊕⊕ High	
		$\leq$ 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	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	
mortality		> 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	
	Follow-up	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)#	1 more per 1000 (-1 to 3)	$\oplus \oplus \oplus \oplus$ High	
	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)	$\oplus \oplus \oplus \oplus$ High	

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

		>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)	$\oplus \oplus \oplus \oplus$ High
		Healthy population (4)	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	733/43925 (1.67%)	640/42275 (1.51%)	1. 06 (0.86 to 1.31)*	2 more per 1000 (0 to 3)	⊕⊕⊕O 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)*	1 fewer per 1000 (-6 to 4)	⊕⊕⊕⊕ High
	Study populations	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)*	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)*	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)*	3 fewer per 1000 (-17 to 11)	⊕⊕⊕⊕ High
		$\leq$ 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)	$\oplus \oplus \oplus \oplus$ High
		1-5 years (19)	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	2432/36741 (6.76%)	2154/34270 (6.59%)	$0.97 (0.88 \text{ to } 1.08)^*$	4 more per 1000 (0 to 7)	⊕⊕⊕O Moderate
	Follow-up duration	5-10 years (7)	No serious	No serious	No serious	No serious	Undetected	1967/29549 (6.65%)	1904/27883 (6.41%)	$0.96 (0.90 \text{ to } 1.02)^*$	2 fewer per 1000 (-6 to 2)	$\oplus \oplus \oplus \oplus$ High
All-cause		>10 years (2)	No serious	No serious	No serious	No serious	Undetected	826/30971 (2.67%)	869/30976 (2.81%)	$0.95 (0.87 \text{ to } 1.04)^*$	1 fewer per 1000 (-4 to 1)	$\oplus \oplus \oplus \oplus$ High
mortality		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)	$\oplus \oplus \oplus \oplus$ 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)	$\oplus \oplus \oplus \oplus$ High
	Study populations	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)	$\oplus \oplus \oplus \oplus$ 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
Total cancer incidence (7)	Dose of aspirin	Aminin < 100m - / L. fam	No serious	Serious <sup>e</sup>	No serious	No serious	Undetected	3311/44813 (7.39%)	3252/44852 (7.25%)	1.01 (0.93 to 1.10)*	1 more per 1000 (-2 to 5)	⊕⊕⊕O Moderate
Total cancer mortality (7)	and Follow- up duration	Aspirin $\leq 100$ mg/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)*	1 fewer per 1000 (-3 to 1)	⊕⊕⊕⊕ High
All-cause mortality (8)	up duration		No serious	No serious	No serious	No serious	Undetected	2340/47361 (4.94%)	2433/47392 (5.13%)	$0.96 (0.91 \text{ to } 1.02)^*$	2 fewer per 1000 (-5 to 1)	$\oplus \oplus \oplus \oplus$ High
		$\leq$ 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
Major bleeding	Dose of aspirin	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
events		> 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)#	5 more per 1000 (3 to 6)	$\oplus \oplus \oplus \oplus$ High

		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
		$\leq$ 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)*	13 more per 1000 (10 to 15)	⊕⊕⊕⊕ High
	Dose of aspirin	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)*	60 more per 1000 (50 to 70)	⊕⊕⊕⊕ High
Total bleeding		> 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)*	16 more per 1000 (10 to 22)	⊕⊕⊕O Moderate
events		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
	Follow-up duration	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)#	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. # fixed-effects model, \* 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.

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

## **Supplementary Table 3:** Sensitivity analyses

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

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