	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
de Lorgeril 1999	?	?	•	•	•
Estruch 2018	•		•	•	•
Singh 2002	?	?	•	•	•

Supplemental figure 1. Risk of bias assessment for randomized clinical trials

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in	total car	rdiovascul	ar disease incide	nce
de Lorgeril et al., 1999	44	605	12.7%	0.28 [0.15, 0.53]	-	- <u>-</u> 1			
Estruch et al., 2018	288	7,447	87.3%	0.70 [0.55, 0.89]		-			
Total (95% CI)	332	8,052	100%	0.62 [0.50, 0.78]		•			
Heterogeneity: $Chi^2 = 7.07$, $df = 1$ (P = 0.008);	$I^2=86\%$								
Test for overall effect: $Z = 4.12 (P < 0.0001)$					0.2	1	5		
					Benefit		Harm		

Supplemental figure 2. Effect of Mediterranean diet on total cardiovascular disease incidence risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in total cardivoascular disease mortality
de Lorgeril et al., 1999 Estruch et al., 2018	19 87	605 7.447	21.5% 78.5%	0.35 [0.15, 0.83] 0.80 [0.51, 1.26]	
,		,		. , .	_
Total (95% CI)	106	8,052	100%	0.67 [0.45, 1.00]	•
Heterogeneity: Chi ² = 2.79	$0, \mathbf{df} = 1 \ (\mathbf{P}$	$= 0.09$); $I^2 = 64$	1%		+ + + + +
Test for overall effect: Z =	1.95 (P =	0.05)			0.1 0.2 0.5 1 2
					Benefit Harm

Supplemental figure 3. Effect of Mediterranean diet on total cardiovascular disease mortality risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95%	CI in coronaı	ry heart	disease incidence
Singh et al., 2002	115	1,000	100.0%	0.48 [0.33, 0.71]		-		
Total (95% CI) Heterogeneity: Not applicable	115	1,000	100%	0.48 [0.33, 0.71]		•		
Test for overall effect: $Z = 3.65$ (P = 0.	.0003)				0.1 0.2 Repetit	0.5 1	2 Iarm	

Supplemental figure 4. Effect of Mediterranean diet on coronary heart disease incidence risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participants Weigl	t RR [95% CI]	RR, 95% CI in coronary heart disease mortality
Singh et al., 2002	22	1,000 100.0	% 0.33 [0.13, 0.85]	
Total (95% CI) Heterogeneity: Not applicable	22	1,000 1009	6 0.33 [0.13, 0.85]	
Test for overall effect: $Z = 2.30$ (P	= 0.02)			0.1 0.2 0.5 1 2 Benefit Harm

Supplemental figure 5. Effect of Mediterranean diet on coronary heart disease mortality risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participants	Weight	RR [95% CI]	R	R, 95% (CI in s	troke incidence
Estruch et al., 2018	139	7,447	100.0%	0.58 [0.42, 0.81]		-	-	
Total (95% CI)	139	7,447	100%	0.58 [0.42, 0.81]		•	>	
Heterogeneity: Not Test for overall effe					0.2 Renef	0.5	1	2 Harm

Supplemental figure 6. Effect of Mediterranean diet on total stroke incidence risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in myocardial infarction incidence
Singh et al., 2002	93	1,000	47.7%	0.52 [0.34, 0.80]	— —
Estruch et al., 2018	106	7,447	52.3%	0.80 [0.53, 1.21]	
Total (95% CI)	199	8,447	100%	0.65 [0.49, 0.88]	•
Heterogeneity: Chi ² =	2.00, df = 1	$(P = 0.16); I^2 =$	50%		
Test for overall effect	z = 2.80 (P)	= 0.005)			0.2 0.5 1 2
					Renefit Harm

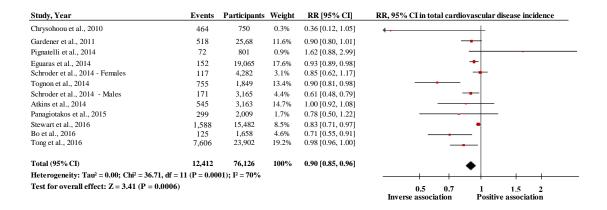
Supplemental figure 7. Effect of Mediterranean diet on myocardial infarction incidence risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participant	s Weight	RR [95% CI]	RR, 95% CI in	myoca	rdial infa	arction mortality
Singh et al., 2002	29	1,000	100.0%	0.67 [0.31, 1.43]			+	
Total (95% CI)	29	1,000	100%	0.67 [0.31, 1.43]	-		-	
Heterogeneity: Not applic	able				+	+	+	
Test for overall effect: Z =	= 1.04 (P = 0.3)	0)			0.1 0.2 0.5	1	2	
					Benefit		Harm	

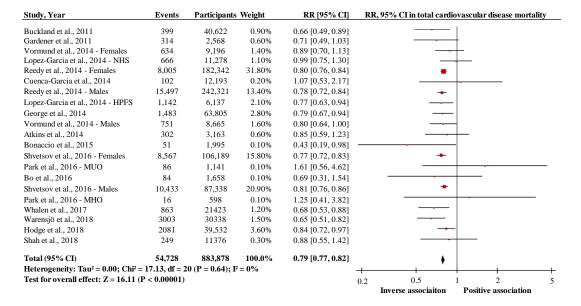
Supplemental figure 8. Effect of Mediterranean diet on myocardial infarction mortality risk. The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I^2 statistic

Study, Year	Events	Participants	Weight	RR [95% CI]	RR,	95% CI in t	otal ca	rdiovascular	disease incider	ıce
Chrysohoou et al., 2010	464	750	4.00%	0.43 [0.19, 0.97]						
Gardener et al., 2011	518	2,568	16.80%	0.80 [0.60, 1.06]			•			
Eguaras et al., 2014	152	19,065	5.60%	1.61 [0.83, 3.11]			+	-		
Atkins et al., 2014	545	3,163	6.00%	0.47 [0.25, 0.89]	i —	•	-			
Pignatelli et al., 2014	72	801	18.20%	0.97 [0.75, 1.26]		-	-			
Bo et al., 2016	125	1,658	29.70%	0.97 [0.92, 1.03]			=			
Tong et al., 2016	7,606	23,902	5.90%	0.59 [0.31, 1.12]		-	\pm			
Rifai et al., 2018	276	1,601	13.90%	1.01 [0.72, 1.42]		-		_		
Total (95% CI)	9,758	53,508	100.0%	0.88 [0.74, 1.04]			•			
Heterogeneity: Tau ² = 0	.03: Chi ² :	= 15.00. df = 7	(P = 0.04): F	2 = 53%	+		_			
Test for overall effect: 2		,	(,-	0.2	0.5	1	2	5	
					Inverse	association		Positive as	ssociation	

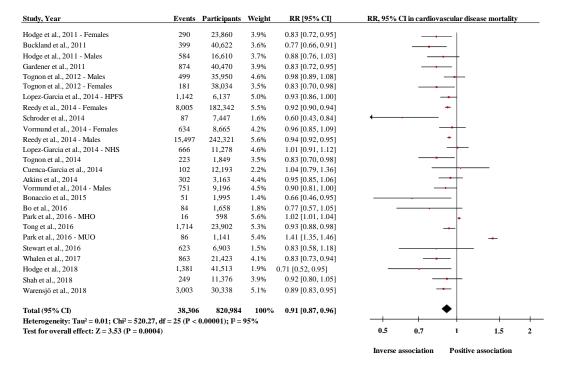
Supplemental figure 9. Association between adherence to Mediterranean diet and total cardiovascular disease incidence (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I^2 statistic.



Supplemental figure 10. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and total cardiovascular disease incidence risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.



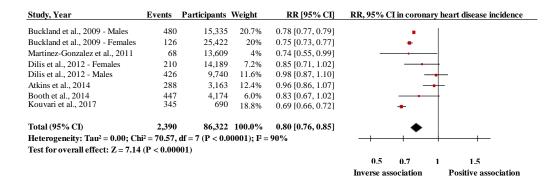
Supplemental figure 11. Association between adherence to Mediterranean diet and total cardiovascular disease mortality risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic.



Supplemental figure 12. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and total cardiovascular disease mortality risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic.RR, relative risk.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in cornary heart disease incidence	e
Buckland et al., 2009 - Males	480	15,335	22.20%	0.58 [0.44, 0.76]		
Buckland et al., 2009 - Females	126	25,422	7.80%	0.67 [0.39, 1.16]		
Martinez-Gonzalez et al., 2011	68	13,609	2.70%	0.42 [0.16, 1.11]		
Dilis 2012 et al., - Females	210	17,189	10.20%	0.62 [0.39, 0.99]		
Dilis 2012 et al., - Males	426	9,740	24.40%	0.90 [0.70, 1.16]	—	
Atkins et al., 2014	288	3,163	15.10%	0.86 [0.60, 1.24]		
Booth et al., 2014	447	4,174	17.50%	0.77 [0.55, 1.07]		
Total (95% CI)	2,045	88,632	100.00%	0.73 [0.62, 0.86]	•	
Heterogeneity: Tau ² = 0.01; Chi ²	= 8.06. df =	6 (P = 0.23):	$I^2 = 26\%$		+	
Test for overall effect: Z = 3.81 (1 - 20,0		0.2 0.5 1 2	
					Inverse association Positive association	

Supplemental figure 13. Association between adherence to Mediterranean diet and coronary heart disease risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I² statistic.



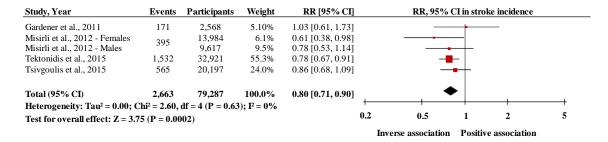
Supplemental figure 14. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and coronary heart disease incidence risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95	% CI in cornary	heart disease mortality
Chiuve et al., 2011	321	81,722	9.10%	0.60 [0.43, 0.84]		-	-
Dilis et al., 2012 - Males	150	9,740	1.50%	0.39 [0.17, 0.89]		-	
Dilis et al., 2012 - Females	90	14,189	4.80%	0.62 [0.39, 0.98]	-	•	—
Bertoia et al., 2014	237	93,122	6.90%	0.67 [0.46, 0.98]			
Hodge et al., 2018	140	39,532	23.00%	0.81 [0.66, 1.00]			-
Warensjö et al., 2018	1081	32,260	54.80%	0.95 [0.83, 1.09]			-
Total (95% CI)	2,019	270,565	100.00%	0.73 [0.59, 0.89]		•	▶
Heterogeneity: $Tau^2 = 0.04$;	$Chi^2 = 13.42$	2, df = 5 (P = 0)	$.02$); $I^2 = 63\%$	•	+		+
Test for overall effect: $Z = 3$.03 (P = 0.0)	02)			0.2	0.5	1 2
					Inverse a	ssociation	Positive association

Supplemental figure 15. Association between adherence to Mediterranean diet and coronary heart disease mortality risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi2) at a significance level of P < 0.10, and quantified by the I2 statistic.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in coronary heart disease mortality
Bertoia et al., 2014	237	93.122	4.9%	0.85 [0.74, 0.99]	- 1
Chiuve et al., 2011	321	81.722	3%	0.73 [0.61, 0.88]	
Dilis et al., 2012 - Females	90	9,740	1%	0.75 [0.57, 0.98]	
Dilis et al., 2012 - Males	150	14,189	2.5%	0.81 [0.66, 0.99]	
Hodge et al., 2018	1040	41513	25.3%	0.90 [0.85, 0.96]	-
Warensjö et al., 2018	1081	30338	62.7%	0.98 [0.95, 1.02]	•
Total (95% CI)	2,919	270,624	100.0%	0.94 [0.91, 0.97]	• • • • • • • • • • • • • • • • • • •
Heterogeneity: Chi ² = 20.66	, df = 5 (P =	0.0009); $I^2 = 76$	5%		
Test for overall effect: $Z = 3$.85 (P = 0.0)	001)			0.5 0.7 1 1.5
					Inverse association Positive association

Supplemental figure 16. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and coronary heart disease mortality risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance fixed-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.



Supplemental figure 17. Association between adherence to Mediterranean diet and stroke incidence risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in stroke incidence
Gardener et al., 2011	171	2,568	6.5%	1.00 [0.82, 1.22]	
Misirli et al., 2012 - Males	204	9,617	8%	0.88 [0.74, 1.04]	
Misirli et al., 2012 - Females	191	13,984	7%	0.81 [0.67, 0.98]	
Schroder et al., 2014	139	7,447	3.6%	0.73 [0.55, 0.98]	
Tognon 2014	167	1,849	6.8%	0.93 [0.77, 1.13]	
Tektonidis et al., 2015	1,532	32,921	23.8%	0.90 [0.84, 0.96]	
Lau et al., 2015	13	274	0.2%	0.27 [0.08, 0.91]	
Tsivgoulis et al., 2015	565	20,197	19.6%	0.93 [0.85, 1.01]	
Stewart et al., 2016	267	6,903	1.0%	0.56 [0.32, 0.96]	
Tong et al., 2016	1,023	23,902	23.0%	0.96 [0.89, 1.02]	-• +
Total (95% CI)	4,272	119,662	100.0%	0.90 [0.85, 0.96]	•
Heterogeneity: Tau ² = 0.00; C	$Chi^2 = 13.77, c$	df = 9 (P = 0.13)	3); $I^2 = 35\%$		
Test for overall effect: Z = 3.5	54 (P = 0.000)	4)			0.5 0.7 1 1.5
					Inverse association Positive association

Supplemental figure 18. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and stroke incidence risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in stroke mortality		
Misirli 2012 Males	196	13,984	2.60%	0.88 [0.50, 1.55]			
Misirli 2012 Females	170	9,617	1.90%	0.60 [0.31, 1.16]			
Aigner 2018 - Males	1,746	80,380	54.10%	0.88 [0.78, 1.00]			
Aigner 2018 - Females	1,802	91,663	41.30%	0.88 [0.76, 1.01]		-	
Total (95% CI)	3,744	195,644	100.00%	0.87 [0.80, 0.96]		•	
Heterogeneity: Chi ² = 1.27, df = 3	(P = 0.74); 1	$I^2 = 0\%$			0.2 0.5	1 2	
Test for overall effect: $Z = 2.90$ (P	0 = 0.004				Inverse association	Positive association	

Supplemental figure 19. Association between adherence to Mediterranean diet and stroke mortality risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in stroke mortality			
Misirli et al., 2012 - Females	104	13,984	9.7%	0.82 [0.64, 1.06]				
Misirli et al., 2012 - Males	92	9,617	8.7%	0.94 [0.72, 1.23]				
Tognon et al., 2012 - Females	65	38,034	8.9%	1.00 [0.77, 1.30]				
Tognon et al., 2012 - Males	79	35,950	9.7%	0.96 [0.75, 1.24]				
Tognon et al., 2014	40	1,849	3.7%	1.05 [0.70, 1.59]				
Tong et al., 2016	509	23902	59.3%	0.98 [0.88, 1.08]	- ₱			
Total (95% CI)	889	123,336	100.0%	0.96 [0.89, 1.04]				
Heterogeneity: Tau ² = 0.00; Chi ² = 1.94, df = 5 (P = 0.86); F = 0%								
Test for overall effect: $Z = 0$.	99 (P = 0.3	32)			0.7 1 1.5			
				,	Inverse association Desitive association			

Supplemental figure 20. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and stroke mortality risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.

Study, Year	Participants	Weight	RR [95% CI]]	RR, 95% CI in myocar	dial infarction incidence	
Gardener et al., 2011	133	2,568	11.5%	0.65 [0.38, 1.12]		-	+
Tektonidis et al., 2015	1,109	32,921	88.5%	0.74 [0.61, 0.90]		-	
Total (95% CI)	1,242	35,489	100.0%	0.73 [0.61, 0.88]		•	
Heterogeneity: Chi ² = 0.20	0, df = 1 (P = 0)	0.66); $I^2 = 0\%$			-		
Test for overall effect: Z =	3.38 (P = 0.0	007)			0.2	0.5	1 2
						Inverse association	Positive association

Supplemental figure 21. Association between adherence to Mediterranean diet and total myocardial infarction risk (high vs low categories). The diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I² statistic.

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95% CI in myocardial infarction incidence				
Gardener et al., 2011	133	2,568	17.6%	0.88 [0.71, 1.10]					
Schroder et al., 2014	106	7,447	13.1%	0.61 [0.45, 0.84]		•			
Tognon et al., 2014	161	1,849	18.8%	0.81 [0.67, 0.99]		-	_		
Tektonidis et al., 2015	1,109	32,921	12.1%	0.59 [0.41, 0.83]					
Tong et al., 2016	2,967	23,902	25.4%	0.97 [0.92, 1.01]			-		
Stewart et al., 2016	698	6,903	13.0%	0.78 [0.56, 1.07]	-	-	+		
Total (95% CI)	5,174	75,590	100.0%	0.79 [0.67, 0.94]		•	-		
Heterogeneity: Tau ² = 0.03; Chi	P = 19.13, $df = 5$ (P	$= 0.002$); $I^2 = 7$	4%						
Test for overall effect: $Z = 2.75$	(P = 0.006)				0.5	0.7	1	1.5	2
					Inverse	association	Positiv	e associati	ion

Supplemental figure 22. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and myocardial infarction incidence risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance random-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk

Study, Year	Events	Participants	Weight	RR [95% CI]	RR, 95	5% CI in myocaro	lial infarction mortality
Tognon et al., 2012 - Females	61	38,034	4.0%	0.73 [0.55, 0.99]	_	-	-
Tognon et al., 2012 - Males	244	35,950	21%	0.85 [0.74, 0.96]			-
Tognon et al., 2014	64	1,849	21%	0.85 [0.74, 0.96]			-
Tong et al.,2016	817	23,902	53%	0.90 [0.83, 0.98]		-	-
Total (95% CI) Heterogeneity: Chi ² = 2.32, df		1); $I^2 = 0\%$	100.0%	0.87 [0.82, 0.92]	0.5	0.7	1 1.5
Test for overall effect: $Z = 4.6$	6 (P < 0.0000	01)				***	
					In	verse association	Positive association

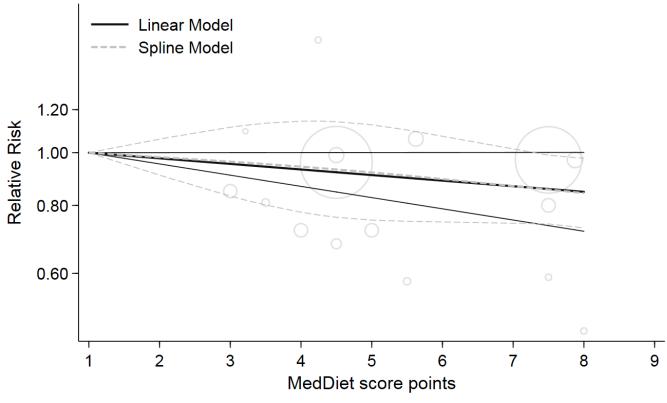
Supplemental figure 23. Forest plots for all prospective cohort studies assessing the association between 2-point increase in the adherence to the Mediterranean diet and myocardial infarction mortality risk. Data are expressed as relative risk and 95% confidence interval by using generic inverse-variance fixed-effects model. Diamond represents the pooled effect estimates. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi²) at a significance level of P < 0.10, and quantified by the I^2 statistic. RR, relative risk.

Subgroup	Level	No. of Trials	N	·	·	RR [95	% CI] on card	iovascular diseas	e mortality		·	Residual I ² [%]	P-Value
				Within Subgroups				·	·		Between Subgroups		
Total		21	883,878	0.79 [0.77, 0.82]		-							
Sex	Females [1]	6	403,148	0.78 [0.74, 0.82]							1 vs 2: 0.97 [0.91,1.04]	0	0.51
	Males [2]	5	347,624	0.80 [0.77, 0.84]							1 vs 3: 1.00 [0.89,1.13]		
	Mixed [3]	10	133,106	0.78 [0.70, 0.87]		•					2 vs 3: 1.03 [0.92,1.16]		
Follow-up	<13.4 years	11	204,374	0.79 [0.73, 0.86]		-					1.00 [0.91, 1.10]	0	0.93
·	≥13.4 years	10	679,504	0.79 [0.77, 0.82]		-							
NOS scale	<7	2	94,143	0.79 [0.64, 0.86]	_		_				1.08 [0.93, 1.25]	0	0.31
	≥7	19	789,735	0.80 [0.77, 0.82]		+							
MedDiet Score	Trichopolou original 9 points [1]	5	29,790	0.75 [0.58, 0.98]		•					1 vs 2: 0.95 [0.73,1.24]	0	0.30
method	Adapted from Trichopolou original [2]	13	830,926	0.79 [0.77, 0.82]							1 vs 3: 1.03 [0.71,1.49]		
	Others [3]	3	23,162	0.73 [0.57, 0.95]	· 				•		2 vs 3: 1.09 [0.84,1.41]		
Population	Non-Mediterranean	18	839,603	0.79 [0.77, 0.82]		-					1.25 [0.94,1.66]	0	0.11
	Mediterranean	3	44,275	0.63 [0.48, 0.84]	•								
					0.5	0.75	1	1.25	1.5	1.75			
					Ber	efit		Harm					

Supplemental figure 24. Subgroup analyses of Mediterranean diet and total cardiovascular mortality. NOS means Newcastle-Ottawa Scale. Diamonds for each subgroup levels represents the pooled effect estimates. The dashed line represents the pooled effect estimated for the overall analysis. RR, relative risk.

Subgroup	Level	# Cohort comparison	# Participants		RR [95% CI] in cardiovascular disease mortality		Residual I ²	P-value
				Within subgroups		Between subgroups	_	
Total	-	21	883,878	0.79 [0.77,0.82]	•			
Selection								
1. Representativeness of the exposed cohort	0 points	6	126,097	0.79 [0.71, 0.88]	-	4 04 [0 00 4 42]	0	0.01
	1 point	15	757,781	0.79 [0.77, 0.82]	♦	1.01 [0.90, 1.12]	0	0.91
2. Selection of the non exposed cohort	0 points	0	-	-			0	0.64
	1 point	21	883,878	0.79 [0.77,0.82]	→	-	0	0.64
3. Ascertainment of exposure	0 points	18	829,312	0.79 [0.77, 0.82]	•	0.00 [0.73, 4.43]	0	0.22
·	1 point	3	54,566	0.71 [0.57, 0.89]		0.90 [0.72, 1.13]	0	0.33
4. Demonstration that outcome of interest was not present	0 points	1	1,658	0.69 [0.29, 1.62]		4 45 (0 40 0 74)	•	0.70
at start of study	1 point	20	882,220	0.79 [0.77, 0.82]	•	1.15 [0.49, 2.71]	0	0.73
Outcome								
5. Assessment of outcome	0 points	0	_	_				
	1 point	21	883,878	0.79 [0.77,0.82]	.	-	0	0.64
6. Was follow-up long enough for outcomes to occur	0 points	0	-	-				
	1 point	21	883,878	0.79 [0.77,0.82]	•	-	0	0.64
7. Adequacy of follow-up of cohort	0 points	0	-	-				
	1 point	21	883,878	0.79 [0.77,0.82]	•	-	0	0.64
Comparability								
8. Study controls for primary confounding variable	0 points	0	_	_				
	1 point	21	883,878	0.79 [0.77,0.82]	•	-	0	0.64
9. Study controls for secondary confounding variables	0 points	14	848,527	0.79 [0.77, 0.82]	•			
	1 point	7	35,351	0.85 [0.74, 0.98]	-	1.07 [0.93, 1.25]	0	0.29
					0 1	2		
					Benefit Harm			

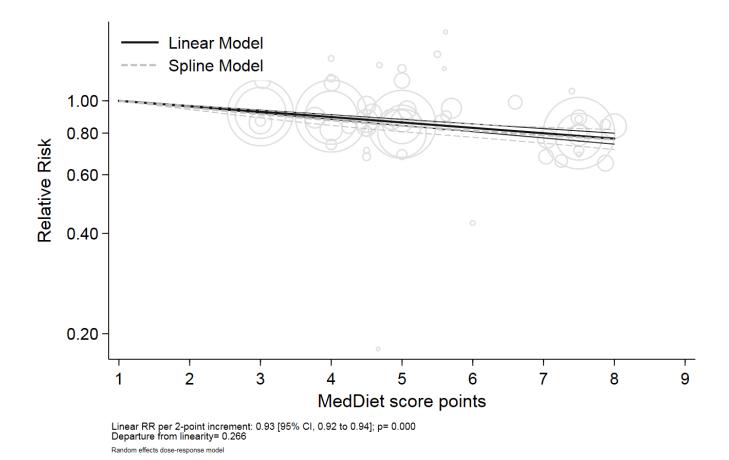
Supplemental figure 25. Risk of bias (using Newcastle-Ottawa Scale [NOS]) subgroup analysis for studies investigating the association of Mediterranean diet adherence and cardiovascular disease mortality. One point was given for comparability if study adjusted for the pre-specified primary confounding variable (age) and a second point if the study adjusted for 4 of the 5 pre-specified secondary variables (gender, physical activity, family history of cardiovascular disease, markers of obesity/overweight and dyslipidemia). Diamonds for each subgroup level represents the pooled effect estimates. The dashed line represents the pooled effect estimates for the overall analysis. RR, relative risk.



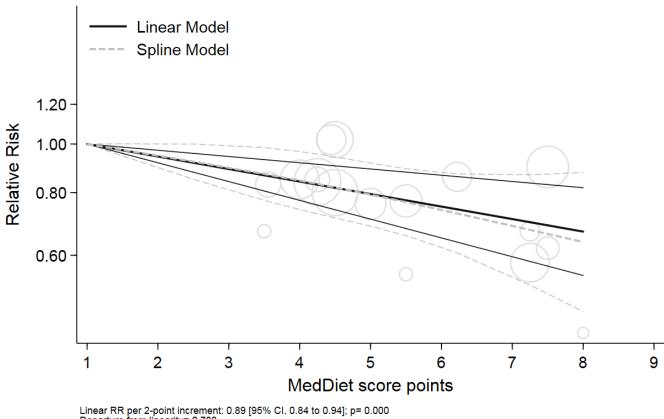
Linear RR per 2-point increment: 0.95 [95% CI, 0.91 to 1.00]; p= 0.052 Departure from linearity= 0.874

Random effects dose-response model

Supplemental figure 26. Linear and non-linear dose-response relation between increasing 2-point of Mediterranean diet score and the risk of total cardiovascular disease incidence (n=6 studies). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.



Supplemental figure 27. Linear and non-linear dose-response relation between increasing 2-point of Mediterranean diet score and the risk of total cardiovascular disease mortality (n=19 studies). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.

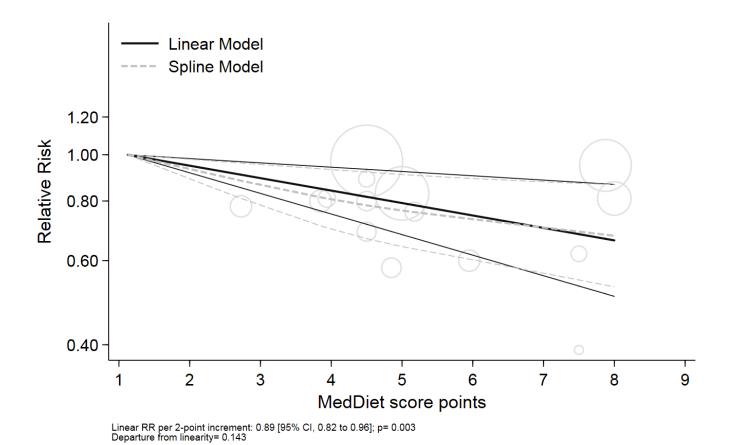


Linear RR per 2-point increment: 0.89 [95% CI, 0.84 to 0.94]; p= 0.000 Departure from linearity= 0.782

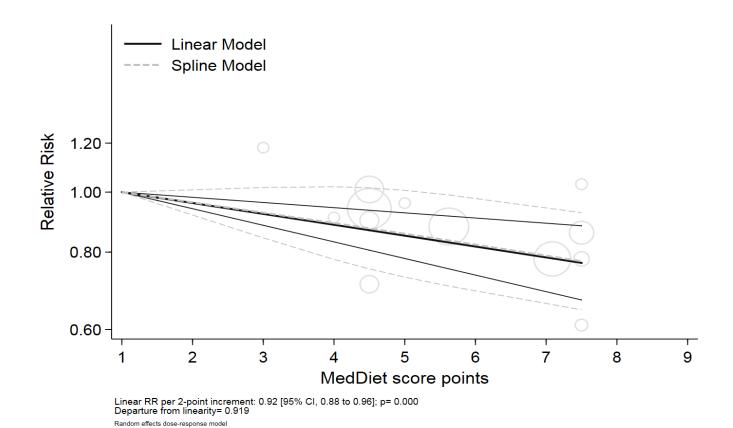
Random effects dose-response model

Supplemental figure 28. Linear and non-linear dose-response relation between increasing 2-point of Mediterranean diet score and the risk of coronary heart disease incidence (n=7 studies). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.

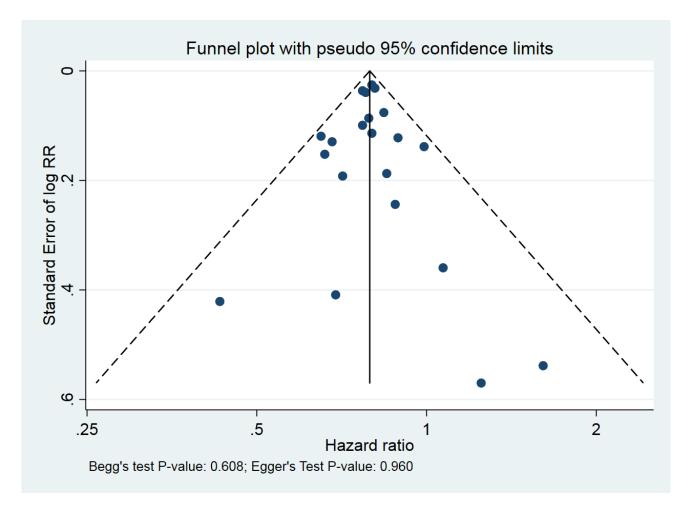
Random effects dose-response model



Supplemental figure 29. Linear and non-linear dose-response relation between increasing 2-point of Mediterranean diet score and the risk of coronary heart disease mortality (n=6 studies). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.



Supplemental figure 30. Linear and non-linear dose-response relation between increasing 2-point of Mediterranean diet score and the risk of stroke incidence (n=5 studies). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.



Supplemental figure 31. Funnel plot of natural logarithm relative risk (RR) for total cardiovascular disease mortality. The vertical line represents the pooled effect estimates expressed as a lnRR. Dash lines represents pseudo-95% confidence intervals. The circles represent risk estimates for each cohort, and the horizontal lines represent standard errors of the lnRR.

	Medline
1	exp Diet, Mediterranean/
	(mediterranean adj3 diet).mp.
	mediterranean diet*.mp.
	or/1-3
	exp Stroke/
	(fatal adj3 stroke).mp.
	non fatal stroke.mp.
	hemorrhagic stroke.mp.
	exp Intracranial Hemorrhages/
	exp Intracranial arterial diseases/
	ischemic stroke.mp.
	exp Brain Ischemia/
	exp Cerebral Infarction/
	exp Peripheral Arterial Disease/
	peripheral artery disease.mp.
	exp Heart Failure/
	heart failure.mp.
	exp myocardial ischemia/
	exp myocardial infarction/
	cardiovascular disease mortality.mp.
	cardiovascular disease death.mp.
	CVD death.mp.
	CVD mortality.mp.
	cardiovascular disease.mp.
	exp cardiovascular disease/
	CVD.mp.
	coronary disease.mp.
	exp Coronary Disease/
	cerebrovascular.mp.
	cerebral vascular.mp.
	or/5-30
	exp cohort studies/
	cohort\$.tw.
	controlled dinical trial.pt.
	epidemiologic methods/
	limit 35 to yr=1971-1988
	32 or 33 or 34 or 36
	4 and 31 and 37
	"randomized controlled trial".pt.
40	(random\$ or placebo\$ or single blind\$ or
	double blind\$ or triple blind\$).ti,ab.
	(retraction of publication or retracted
	publication).pt.
42	or/39-41
43	(animals not humans).sh.
	((comment or editorial or meta-analysis or
	practice-guideline or review or letter or
	journal correspondence) not "randomized
44	controlled trial").pt.
	(random sampl\$ or random digit\$ or random
	effect\$ or random survey or random
	regression).ti,ab. not "randomized controlled
45	trial".pt.
	42 not (43 or 44 or 45)
	4 and 31 and 46

	Embase
1	exp Mediterranean diet/
2	(mediterranean adj3 diet).mp.
3	mediterranean diet*.mp.
4	or/1-3
5	exp cerebrovascular accident/
6	stroke.mp.
7	(fatal adj3 stroke).mp.
8	non fatal stroke.mp.
	hemorrhagicstroke.mp.
10	exp brain hemorrhage/
11	intracranial hemorrhage.mp.
	exp cerebral artery disease/
13	intracranial arterial disease.mp.
14	ischemic stroke.mp.
	exp brain ischemia/
	exp brain infarction/
17	exp peripheral occlusive artery disease/
	peripheral artery disease.mp.
	exp heart failure/
	heart failure.mp.
	exp heart muscle ischemia/
	exp heart infarction/
	cardiovascular disease mortality.mp.
	cardiovascular disease death.mp.
	CVD mortality.mp.
	CVD death.mp.
	cardiovascular disease.mp.
	exp cardiovascular disease/
	CVD.mp.
	coronary disease.mp.
	exp coronary artery disease/
	cerebrovascular.mp.
	cerebral vascular.mp.
	or/5-33
	exp cohort analysis/
	explongitudinal study/
	exp prospective study/
	exp follow up/
	cohort\$.tw.
	or/35-39
	4 and 34 and 40
42	(random\$ or placebo\$ or single blind\$ or
42	double blind\$ or triple blind\$).ti,ab. RETRACTED ARTICLE/
	or/42-43 (animal\$ not human\$).sh,hw.
43	(book or conference paper or editorial or
	letter or review).pt. not exp randomized
16	controlled trial/
40	(random sampl \$ or random digit \$ or random
	effect\$ or random survey or random
	maraccian) ti ab not ava randomizad

1 Diet, Mediterranean/
2 (mediterranean adj3 diet).mp
3 mediterranean diet*.mp.
4 or/1-3
5 Stroke/
6 stroke.mp.
7 cerebrovas cular accident.mp.
8 (fatal adj3 stroke).mp.
9 Cerebral Hemorrhage/
10 hemorrhagic stroke.mp.
11 Intracranial Hemorrhages/
12 Brain Ischemia/
13 brain ischemia.mp.
14 Cerebral Infarction/
15 Peripheral Arterial Disease/
16 peripheral arterial disease.mp.
17 Heart Failure/
18 Myocardial Ischemia/
19 myocardial ischemia.mp.
20 Myocardial Infarction/
21 myocardial infarction.mp.
22 cardiovascular disease mortality.mp.
23 cardiovascular disease death.mp.
24 CVD mortality.mp.
25 Cardiovascular Diseases/
26 cardiovas cular diseas e.mp.
27 CVD.mp.
28 Coronary Disease/
29 coronary disease.mp.
30 cerebrovas cular.mp.
31 or/5-30
32 4 and 31

Cochrane

Supplemental Table 1. Search strategy. The original search date was January 16, 2017 for MEDLINE and EMBASE databases and February 9, 2017 for the Cochrane Library Database. Updated searches were performed on April 20, 2018 and May 7, 2018, respectively.

47 controlled trial/ 48 44 not (45 or 46 or 47) 49 4 and 34 and 48 50 41 or 49

regression).ti,ab. not exp randomized

Supplemental Table 2: Newcastle-Ottawa Scale (NOS) assessment for the quality of cohort studies.

Studies.	C . 1	O 4h	C	77 . 4 . 1d
Study	Selectiona	Outcome ^b	Comparability ^c	Total ^d
Buckland et al,	4	3	2	9
2009		4		
Chrysohoou et al,	2	1	2	5
2010				0
Buckland et al,	4	3	1	8
2011				
Chiuve et al, 2011	2	3	1	6
Gardener et al,	4	3	1	8
2011				
Martinez-	3	3	2	8
Gonzalez et al,				
2011				
Dilis et al, 2012	4	3	1	8
Misirli et al, 2012	4	3	1	8
Tognon et al,	3	2	1	6
2012				
Atkins et al, 2014	2	3	2	7
Bertoia et al, 2014	2	3	1	6
Booth et al, 2014	2	3	1	6
Cuenca-Garcia et	3	3	1	7
al, 2014				
George et al, 2014	2	3	1	6
Lopez-Garcia et	2	3	2	7
al, 2014				
Reedy et al, 2014	3	3	1	7
Schroder et al,	4	3	2	9
2014				
Tognon et al,	3	3	1	7
2014				
Vormund et al,	3	3	1	7
2014				
Bonaccio, et al	3	3	1	7
2015				
Eguaras et al,	2	3	1	6
2015				
Lau et al, 2015	1	3	2	6
Panagiotakos et	3	3	2	8
al, 2015			_	_
Pignatelli et al,	1	3	1	5
2014	-			
Tektonidis, et al	3	3	2	8
2015				
Tsivgoulis et al,	3	3	1	7
2015			_	,
Bo et al, 2016	2	3	2	7
Park et al, 2016	3	3	2	8
Shvetsov et al,	3	3	1	7
2016	3		1	'
Stewart et al,	2	2	2	6
2016	2			
Tong et al, 2016	3	3	2	8
Kouvari et al,	2	3	2	7
2017	<u> </u>	3		'
2017		<u> </u>	1	

Whalen et al, 2017	3	3	1	7
Hodge et al, 2018	3	3	1	7
Shah et al, 2018	3	3	2	Q
	2	2	1	6
Warensjö et al, 2018	2	3	1	O
Rifai et al, 2018	2	3	1	6
Aigner et al, 2018	3	3	1	7

^aMaximum of 4 points could be given for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline

^bMaxium of 3 points could be given for follow-up length, adequacy of follow-up and outcome assessment

 $^{^{}c}$ Maximum of 2 points could be given for controlling for the pre-specified primary confounding (age) and \geq 4 of the secondary confounding variables (sex, family history of cardiovascular disease, physical activity, markers of obesity/overweight and dyslipidemia)

^dA maximum of 9 points could be given

Supplemental Table 3: Significant results of sensitivity analysis by the systematic removal of one study at a time from the analysis^a.

Removal of	RR	95% CI	P-value*	\mathbf{I}^2	P-heterogeneity**	Comment		
Total CVD incidence								
Eguaras et al., 2014	0.92	(0.79, 1.07)	0.27	41	0.12	Heterogeneity was explained		
CHD mortality								
Warensjo et al., 2018	0.70	(0.61, 0.82)	< 0.01	19	0.30	Heterogeneity was explained		

^aSensitivity analysis consisted in the removal of a single study at a time from the meta-analyses and recalculating the summary relative risk. A comparison whose removal changed the significance of the heterogeneity, or changed the significance, direction or magnitude (by more than 20%) of the pooled effect estimate, was considered as influential. Only comparisons that are influential are presented in the table.

CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; I2, Heterogeneity; RR, Relative risk.

^{*}p<0.05 is considered significant.

^{** &}lt; 0.10 is considered significant

Supplemental Table 4 GRADE assessment of the systematic review and meta-analysis of randomized clinical trials assessing the effect of the Mediterranean diet on cardiovascular disease outcomes

Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Quality
Total cardiovascular disease incidence	2	randomized trials	not serious	serious ^a	not serious	not serious	none	RR 0.62 (0.50 to 0.78)	⊕⊕⊕○ MODERATE
Total cardiovascular disease mortality	2	randomized trials	not serious	serious ^b	not serious	serious ^c	none	RR 0.67 (0.45 to 1.00)	⊕⊕⊖⊖ LOW
Coronary heart disease incidence	1	randomized trials	serious ^d	not serious	serious ^e	not serious	none	RR 0.48 (0.33 to 0.70)	⊕⊕⊖⊖ LOW
Coronary heart disease mortality	1	randomized trials	serious ^f	not serious	serious ^g	not serious	none	RR 0.33 (0.13 to 0.85)	⊕⊕⊖⊖ LOW
Stroke incidence	1	randomized trials	not serious	not serious	serious ^h	not serious	none	RR 0.58 (0.42 to 0.81)	⊕⊕⊕○ MODERATE
Myocardial infarction incidence	2	randomized trials	seriousi	not serious	not serious	not serious	none	RR 0.65 (0.49 to 0.88)	⊕⊕⊕⊖ MODERATE
Myocardial infarction mortality	1	randomized trials	serious ^j	not serious	serious ^k	serious ¹	none	RR 0.67 (0.31 to 1.43)	⊕○○○ VERY LOW

CI: Confidence interval; RR: Risk ratio

a. Serious inconsistency for total cardiovascular disease events risk due to high heterogeneity (I²=86%, P=0.007)

b. Serious inconsistency for cardiovascular mortality risk due to high heterogeneity (I²=67%, P=0.08)

c. Serious imprecision for cardiovascular mortality, as the 95% CIs (0.47, 1.02) overlap with the minimally important difference of 5% (RR 0.95 to 1.05)

d. Serious risk of bias for coronary heart disease events risk, since there is only one study which also appears to have unreliable data.

e. Serious indirectness for coronary heart disease events risk, as there is only 1 available study which also appears to have unreliable data

f. Serious risk of bias for coronary heart disease mortality risk, since there is only one study which also appears to have unreliable data.

g. Serious indirectness for coronary heart disease mortality risk, as there is only 1 available study which also appears to have unreliable data

- h. Serious indirectness for stroke events risk, as there is only 1 available study
- i. Serious risk of bias for MI events risk, since there are only 2 studies and 1 of them (Singh et al,) appears to have unreliable data
- j. Serious risk of bias for MI mortality, since there is only one study which also appears to have unreliable data
- k. Serious indirectness for MI mortality risk, as there is only 1 available study which also appears to have unreliable data
- 1. Serious imprecision for MI mortality risk, as the 95% CIs (0.31, 1.43) include both clinically important benefit (RR 0.95) and harm (RR 1.05)

Supplemental Table 5. GRADE assessment of the systematic review and meta-analysis of prospective cohort studies assessing the association between Mediterranean diet adherence and cardiovascular disease outcomes.

Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Quality
Total cardiovascular disease incidence	8	observational studies	not serious	not serious ^a	not serious	serious ^b	none	RR 0.88 (0.74 to 1.04)	⊕○○○ VERY LOW
Total cardiovascular disease mortality	21	observational studies	not serious	not serious	not serious	not serious	dose response gradient	RR 0.79 (0.77 to 0.82)	⊕⊕⊕○ MODERATE
Coronary heart disease incidence	7	observational studies	not serious	not serious	not serious	not serious	dose response gradient	RR 0.73 (0.62 to 0.86)	⊕⊕⊕○ MODERATE
Coronary heart disease mortality	6	observational studies	serious ^c	not serious ^d	not serious	not serious	dose response gradient	RR 0.83 (0.75 to 0.92)	⊕⊕⊖⊖ Low
Stroke incidence	5	observational studies	not serious	not serious	serious ^e	not serious	dose response gradient	RR 0.80 (0.71 to 0.90)	⊕⊕○○ LOW
Stroke mortality	4	observational studies	not serious	not serious	not serious	serious ^f	none	RR 0.87 (0.80 to 0.96)	⊕○○○ VERY LOW
Myocardial infarction incidence	2	observational studies	not serious	not serious	serious ^g	not serious	none	RR 0.73 (0.61 to 0.88)	⊕○○○ VERY LOW

CI: Confidence interval; RR: Risk ratio

a. Although there was high heterogeneity (I^2 =53%, p=0.04), we did not downgrade for inconsistency because removal of one study (Eguaras et al. 2014) explained some of the heterogeneity (I^2 =41%, p=0.12)

b. Serious imprecision as the 95%CIs (0.74, 1.04) overlap with the minimally important difference of 5% (RR 0.95 to 1.05)

c. Serious risk of bias for coronary heart disease mortality risk, as 50% of the studies were low-quality (NOS<7)

d. Although there was high heterogeneity (I²=53%, p=0.02), we did not downgrade for inconsistency because removal of one study (Warensjo et al. 2018) explained some of the heterogeneity (I²=19%, p=0.30)

e. Serious indirectness as studies contributing >50% of the weight (64.1%) were conducted in females.

f.. Serious imprecision as the 95%CIs (0.80, 0.96) overlap with the minimally important difference of 5% (RR 0.95 to 1.05)

g. Serious indirectness as 97% of the participants across the 2 studies were female.