Supplementary

Combination of Multiple Low-Risk Lifestyle Behaviors and Incident Type 2 Diabetes: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies

Supplementary table 1. Search Strategy

Database and Search Terms		
MEDLINE 1. Health Behavior/ 2. life style/ 3. life change events/ 4. risk reduction behavior/ 5. Lifestyle*.tw 6. Life Style*.tw 7. Low Risk adj2 Behavio?r*.tw 8. Health* adj2 Behavio?r*.tw 9. Habit*.tw 10. Diabetes Mellitus, Type 2/ 11. Type 2 adj7 diabet*.tw 12. Type ii adj7 diabet*.tw 13. Type 2 adj1 dm.tw 14. Type ii adj1 dm.tw 15. Non-insulin dependent diabetes.tw 16. Adult-onset diabetes.tw 17. Maturity-onset diabetes.tw 18. T2D*.tw 19. DM2.tw 20. MODY.tw 21. NIDDM.tw 22. risk factors/ 23. Prevent*.tw 24. Risk*.tw 25. exp cohort studies/ 26. cohort$.tw. 27. controlled clinical trial.pt. 28. epidemiologic methods/ 29. limit 28 to yr=1971-1988 30. or/1-9 31. or/10-21 32. or/22-24 33. or/25-27,29 34. 30 and 31 and 32 and 33	EMBASE 1. Health Behavior/ 2. lifestyle/ 3. lifestyle modification/ 4. risk reduction/ 5. Lifestyle*.tw 6. Life Style*.tw 7. Low Risk adj2 Behavio?r*.tw 8. Health* adj2 Behavio?r*.tw 9. Habit*.tw 10. Type 2 adj7 diabet*.tw 11. Type ii adj7 diabet*.tw 12. Type 2 adj1 dm.tw 13. Type ii adj1 dm.tw 14. Non-insulin dependent diabetes mellitus/ 15. Adult-onset diabetes.tw 16. Maturity-onset diabetes.tw 17. T2D*.tw 18. DM2.tw 19. MODY.tw 20. NIDDM.tw 21. risk factor/ 22. Prevent*.tw 23. Risk*.tw 24. exp cohort analysis/ 25. exp longitudinal study/ 26. exp prospective study/ 27. exp follow up/ 28. cohort$.tw. 29. or/1-9 30. or/10-20 31. or/21-23 32. or/24-28 33. 29 and 30 and 31 and 32 34. limit 33 to embase	COCHRANE 1. Health Behavior/ 2. life style/ 3. life change events/ 4. risk reduction behavior/ 5. Lifestyle*.ti,ab,hw 6. Life Style*.ti,ab,hw 7. Low Risk adj2 Behavio?r*.ti,ab,hw 8. Health* adj2 Behavio?r*.ti,ab,hw 9. Habit*.ti,ab,hw 10. Diabetes Mellitus, Type 2/ 11. (Type 2 adj7 diabet*).ti,ab,hw 12. (Type ii adj7 diabet*).ti,ab,hw 13. (Type 2 adj1 dm).ti,ab,hw 14. (Type ii adj1 dm).ti,ab,hw 15. Non-insulindependentdiabetes.ti,ab,hw 16. Adult-onset diabetes.ti,ab,hw 17. Maturity-onset diabetes.ti,ab,hw 18. T2D*.ti,ab,hw 19. DM2.ti,ab,hw 20. MODY.ti,ab,hw 21. NIDDM.ti,ab,hw 22. risk factors/ 23. Prevent*.ti,ab,hw 24. Risk*.ti,ab,hw 25. exp cohort studies/ 26. cohort$.ti,ab,hw 27. controlled clinical trial.pt. 28. epidemiologic methods/ 29. limit 28 to yr=1971-1988 30. or/1-9 31. or/10-21 32. or/22-24 33. or/25-27,29 34. 30 and 31 and 32 and 33

Database	Total
MEDLINE – Sep 7, 2022	2,504
EMBASE – Sep 7, 2022	4,136
Cochrane - Jul 16, 2021	347
Total	6,987

The original search was performed on July 04, 2016; a subsequent updated search was performed on September 7, 2022. Cohort studies were indexed under ‘epidemiological methods’ from 1971 to 1988.

Supplementary table 2- Confounding variables included in 17 prospective cohorts examining the relationship between multiple low-risk lifestyle behaviors and type 2 diabetes incidence

Confounding Variables	Aus Diab (1)	CHS (2)	CKB (3)	DFTJ (4)	EPIC-E3N *(5)*	EPIC-NL (6)	EPIC-Norfolk (7)	EPIC Potsdam (8)	FINRISK (9)	FDPS (10)	Hortega (11)	HPFS (12)	MEC (13)	NIH-AARP (14)	NHSI (12)	NHSII (15)	PHSI (16)	SMHS (17)	SWHS (17)	UK Biobank (18)	VIP (19)	WHS (16)
Timing of exposure measurement	Baseline	Updated	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Updated	Baseline	Updated	Baseline	Baseline	Updated	Updated	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
Adjusted for primary confounding variable: Age		X	X	X	X	X	X	X	NA	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjusted for 4/6 of important adjustments	6/6	4/6	5/6	5/6	4/6	6/6	4/6	4/6	NA	3/6	4/6	5/6	4/6	4/6	5/6	5/6	4/6	4/6	4/6	5/6	4/6	4/6
Sex (also stratified)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adiposity (included as exposure)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking (included as exposure)	X	X	X	X	X	X		X			X	X	X	X	X	X	X			X	X	X
Family history of diabetes	X		X	X		X	X					X			X	X		X	X	X		
Energy intake (included in dietary pattern)	X					X																
Physical activity (included as exposure variable)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Other variables																						

Employment/ Education/Social class	X	X	X	X	X			X	X		X		X	X						X	X	
Menopause			X			X								X	X				X			
Marital Status			X	X										X								
Hypertension	X			X							X		X									
Ethnicity		X										X	X	X	X							
Hyperlipidemia	X			X							X											
Myocardial Infarction												X			X							
Cancer												X			X							
Multivitamin Use												X			X							
Aspirin Use												X			X							
Hormone Use															X							
Mutual Adjustment for Low risk behaviors													X	X		X						
Time Period																X					X	
Medication					X		X				X											

Abbreviations: AusDiab=Australian Diabetes, Obesity and Lifestyle Study, CKB=China Kadoorie Biobank study, DFTJ=Dongfeng-Tongji cohort, NHS = Nurses' Health study, EPIC = European Prospective Investigation into Cancer and Nutrition, MEC=Multiethnic Cohort study, NIH-AARP = National Institutes of Health – American Association of Retired Persons, FDPS = Finnish Diabetes Prevention Study, PHS = Physicians Healthy Study, WHS = Women's Health Study, HPFS = Health Professionals Follow-up Study, VIP = Vasterbotten Intervention Program, S=Smoking, A=Alcohol, B=BMI

Supplementary table 3 – Newcastle Ottawa Scale (NOS) for evaluating the quality of nonrandomized studies

Cohort	Selection*	Comparability†	Outcome‡	Total§
Australian Diabetes, Obesity and Lifestyle Study(1)	3	1	3	7
Cardiovascular Health Study(2)	3	2	3	8
China Kadoorie Biobank(3)	3	2	3	8
Dongfeng-Tongji Cohort(4)	2	2	3	7
EPIC-E3N(5)	3	2	3	8
EPIC-NL(6)	3	2	3	8
EPIC-Norfolk(7)	3	2	3	8
EPIC-Postdam(8)	3	2	3	8
FINRISK Study(9)	NA	NA	NA	NA
Finnish Diabetes Prevention Study(10)	4	1	2	7
Health Professionals Follow-up Study(12)	2	2	3	7
Hortega Study(11)	4	2	3	9
Multiethnic Cohort(13)	3	1	3	7
NIH-AARP Diet and Health Study(14)	4	2	1	7
Nurses' Health Study I(12)	2	2	3	7
Nurses' Health Study II(15)	3	2	3	8
Physicians' Health Study I(16)	2	2	3	7
Shanghai Men's Health Study(17)	4	2	3	9
Shanghai Women's Health Study(17)	4	2	3	9
UK Biobank Study(18)	4	2	3	9
Västerbotten Intervention Programme(19)	4	2	3	9
Women's Health Study(16)	2	2	3	7

*Maximum of 4 points were given for representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at the start of the study.

†Maximum of 2 points were given for controlling for the primary confounding variable (age) and 4 of the 6 secondary variables (Sex, adiposity, smoking, family history, energy intake and physical activity)

‡Maximum of 3 points were given for assessment of outcome, long enough follow up time for an outcome to occur, and adequate mitigation of loss to follow up (<10% loss).

§ A maximum of 9 points were awarded with studies judged high (score ≥7), moderate (score = 6) or low (score ≤5) study quality.

Supplementary table 4 – Influence analysis

	RR [95% CI]	p-value	I^2	p-value
Overall	0.20 [0.17, 0.23]	<0.001	87	<0.001
Removal of				
Australian Diabetes, Obesity and Lifestyle Study (1)	0.19 [0.17, 0.22]	<0.001	87	<0.001
Cardiovascular Health Study (2)	0.20 [0.17, 0.23]	<0.001	87	<0.001
China Kadoorie Biobank Study — F (3)	0.20 [0.17, 0.23]	<0.001	87	<0.001
China Kadoorie Biobank Study — M (3)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Dongfeng-Tongji Cohort (4)	0.19 [0.17, 0.21]	<0.001	76	<0.001
EPIC-E3N Cohort (5)	0.20 [0.17, 0.23]	<0.001	87	<0.001
EPIC-NL (6)	0.19 [0.17, 0.22]	<0.001	87	<0.001
EPIC-Norfolk (7)	0.19 [0.17, 0.22]	<0.001	87	<0.001
EPIC-Potsdam(8)	0.20 [0.18, 0.23]	<0.001	85	<0.001
FINRISK Study — F (9)	0.20 [0.17, 0.23]	<0.001	87	<0.001
FINRISK Study — M (9)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Finnish Diabetes Prevention Study (10)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Health Professionals Follow-up Study(12)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Hortega Study (11)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Multiethnic Cohort — Caucasians — F (13)	0.19 [0.17, 0.23]	<0.001	87	<0.001
Multiethnic Cohort — Caucasians — M (13)	0.19 [0.17, 0.23]	<0.001	87	<0.001
Multiethnic Cohort — Japanese — F (13)	0.19 [0.17, 0.22]	<0.001	87	<0.001
Multiethnic Cohort — Japanese — M (13)	0.19 [0.17, 0.22]	<0.001	87	<0.001
Multiethnic Cohort — Native Hawaiians — F (13)	0.19 [0.17, 0.23]	<0.001	87	<0.001
Multiethnic Cohort — Native Hawaiians — M (13)	0.19 [0.17, 0.22]	<0.001	87	<0.001
NIH-AARP Diet and Health Study — F (14)	0.20 [0.17, 0.23]	<0.001	86	<0.001
NIH-AARP Diet and Health Study — M (14)	0.20 [0.17, 0.23]	<0.001	87	<0.001
Nurses Health Study I (12)	0.20 [0.18, 0.23]	<0.001	84	<0.001
Nurses Health Study II (15)	0.20 [0.17, 0.23]	<0.001	86	<0.001
Physicians Health Study I (16)	0.19 [0.17, 0.22]	<0.001	87	<0.001
Shanghai Men's Health Study (17)	0.19 [0.17, 0.23]	<0.001	87	<0.001
Shanghai Women's Health Study (17)	0.19 [0.16, 0.23]	<0.001	87	<0.001
UK Biobank Study (18)	0.19 [0.17, 0.23]	<0.001	87	<0.001
Västerbotten Intervention Programme(19)	0.19 [0.17, 0.22]	<0.001	87	<0.001
Women's Health Study (16)	0.20 [0.17, 0.23]	<0.001	87	<0.001

The pooled relative risk was recalculated after removal of each independent study. Heterogeneity was assessed with the Cochrane Q statistic (Chi^2) and represented with the I^2 value. Any value of I^2>50% indicates significant heterogeneity. The results were shown using relative risk (RR) with 95% confidence interval

Supplementary table 5 – Grade Assessment

Quality assessment								Study event rates (%)	Effect	Quality Importance
No of studies	Design	Study quality	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		Relative (95% CI)	
Effect of combined low risk lifestyle behaviors on incident type 2 diabetes (follow-up median 13 years)										
30 comparisons (19 cohorts)	observational studies	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	no serious publication bias[5]	Large magnitude of effect[6], Dose-response[7]	75,669/ 1,693,753 (4.5%)	Extreme comparison: RR 0.196 (95% CI, 0.170 to 0.227) Global DRM RR 0.15 [95% CI, 0.12 to 0.18]	⊕⊕⊕⊕ HIGH[8]

1. The overall study quality remained high in all the studies (supplementary table 3) and only one study was not rated. Overall study quality was adjusted to be high.
2. Although heterogeneity was high (I^2 was 87%) which was more than the cut-off of I^2>50%, P_Q<0.10, this inconsistency was not considered to be of concern as the magnitude of the effect remained high, and all individual point estimates were in the same direction across with almost all being lower than an RR ≤0.40. Further explained in the discussion section of the paper.
3. There was no serious indirectness as the outcome assessment was of T2D rather than intermediate markers.
4. There was no serious imprecision as 95% CI of the pooled estimate did not cross minimally important difference of 5% i.e. 0.05 or 0.95.
5. Although there was some evidence of publication bias by formal testing with the Egger test (p=0.06), the trim-and-fill did not impute any missing studies and did not significantly change the pooled estimated. Therefore, the possible publication bias was not considered serious.
6. Upgraded twice for a very large magnitude of effect (pooled RR = 0.196 which is less than RR<0.2 criteria for very large effect size)
4. Upgraded for a significant dose-response association (p<0.001).
5 High ⊕⊕⊕⊕ quality evidence. Starting point for observational studies is low quality; no downgrades and upgraded for evidence of a very large magnitude of effect [+2] and dose-response [+1]) to support the conclusion that adherence to a combination of low-risk lifestyle factors (including healthy body weight, healthy dietary pattern, regular physical activity, smoking abstinence or cessation, and moderate alcohol consumption) lowers type 2 diabetes risk compared with minimum low-risk lifestyle factors.

Supplementary table 6. Important studies exploring low-risk lifestyle behaviors and type 2 diabetes that were not included.

Reference	Reason for exclusion
Hu FB, Manson JE, Stampfer MJ, et al (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345(11):790–797. https://doi.org/10.1056/NEJMoa010492	Duplicate data for Nurses Health Study. So Li 2019 was used.
Shan Z, Li Y, Zong G et al (2018) Rotating night shift work and adherence to unhealthy lifestyle in predicting risk of type 2 diabetes: results from two large US cohorts of female nurses. BMJ 363: k4641	Duplicate data for Nurses Health Study I and Nurses Health Study II from Li 2019 and Li 2015, respectively. Data was less granular (gave 3 score divisions) in this publication so Li 2019 and Li 2015 (gave 4 score divisions) were preferred.
Laaksonen, M.A.; Knekt, P.; Rissanen, H.; Härkänen, T.; Virtala, E.; Marniemi, J.; Aromaa, A.; Heliövaara, M.; Reunanen, A. The relative importance of modifiable potential risk factors of type 2 diabetes: a meta-analysis of two cohorts. European Journal of Epidemiology 2010, 25, 115–124.	Did not include diet and included biomarkers in the score.
Effoe VS, Carnethon MR, Echouffo-Tcheugui JB et al (2017) The American Heart Association ideal cardiovascular health and incident type 2 diabetes mellitus among blacks: the Jackson Heart Study. J Am Heart Assoc 6(6):e005008	Included biomarkers in the score
Fretts AM, Howard BV, McKnight B et al (2014) Life s Simple 7 and incidence of diabetes among American Indians: the Strong Heart Family Study. Diabetes Care 37(8):2240–2245. https://doi. org/10.2337/dc13-2267	Included biomarkers in the score
Joseph JJ, Echouffo-Tcheugui JB, Carnethon MR et al (2016) The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Diabetologia 59(9):1893–1903.	Included biomarkers in the score
Joseph JJ, Echouffo-Tcheugui JB, Talegawkar SA et al (2017) Modifiable lifestyle risk factors and incident diabetes in African Americans. Am J Prev Med 53(5):e165–e174. https://doi.org/10. 1016/j.amepre.2017.06.018	Included other factors like tv watching and sleep disordered breathing in the score.
Liu X, Cui L, Wang A et al (2016) Cumulative exposure to ideal cardiovascular health and incident diabetes in a Chinese population: the Kailuan Study. J Am Heart Assoc 5(9):e004132	Included biomarkers in the score
Nguyen B, Bauman A, Ding D (2017) Incident type 2 diabetes in a large Australian cohort study: does physical activity or sitting time alter the risk associated with body mass index? J Phys Act Health 14(1):13–19.	Diet was not included
Zhang Y, Pan X-F, Chen J, et al. Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. Diabetologia 2019; published online Sept 4. DOI:10.1007/s00125-019-04985-9.	A systematic review and meta-analysis but included biomarkers as part of lifestyle factors.

Tatsumi Y, Ohno Y, Morimoto A, et al. Lifestyle and the risk of diabetes mellitus in a Japanese population. J Behav Med 2013;36:225–33. doi:10.1007/s10865-012-9427-z	Used Breslow's healthy lifestyle factors. Included sleep. However, definition of healthy diet was related to eating breakfast or snacking but not on dietary pattern.
Elwood P, Galante J, Pickering J, et al (2013) Healthy Lifestyles Reduce the Incidence of Chronic Diseases and Dementia: Evidence from the Caerphilly Cohort Study. PLoS One 8(12): e81877. doi:10.1371/journal.pone.0081877	Did not exclude cases of diabetes at baseline
Wakasugi M, Narita I, Iseki K, Asahi K, Yamagata K, Fujimoto S, Moriyama T, Konta T, Tsuruya K, Kasahara M, Shibagaki Y, Kondo M, Watanabe T; Japan Specific Health Checkups (J-SHC) Study Group. Healthy Lifestyle and Incident Hypertension and Diabetes in Participants with and without Chronic Kidney Disease: The Japan Specific Health Checkups (J-SHC) Study. Intern Med. 2022 Mar 5. doi: 10.2169/internalmedicine.8992-21	Definition of healthy diet was related to eating breakfast or snacking but not on dietary pattern.
Han Y, Hu Y, Yu C, Guo Y, Pei P, Yang L, Chen Y, Du H, Sun D, Pang Y, Chen N, Clarke R, Chen J, Chen Z, Li L, Lv J; China Kadoorie Biobank Collaborative Group. Lifestyle, cardiometabolic disease, and multimorbidity in a prospective Chinese study. Eur Heart J. 2021 Sep 7;42(34):3374-3384. doi: 10.1093/eurheartj/ehab413	Duplicate data for China Kadoorie Biobank. So Lv 2017 was used.
Cao Z, Xu C, Yang H, Li S, Wang Y. The Role of Healthy Lifestyle in Cancer Incidence and Temporal Transitions to Cardiometabolic Disease. JACC CardioOncol. 2021 Dec 21;3(5):663-674. doi: 10.1016/j.jaccao.2021.09.016	Duplicate data for UK Biobank. So Wang 2022 was used as it had a larger cohort size.
Li R, Cai M, Qian ZM, Wang X, Zhang Z, Wang C, Wang Y, Arnold LD, Howard SW, Li H, Lin H. Ambient air pollution, lifestyle, and genetic predisposition associated with type 2 diabetes: findings from a national prospective cohort study. Sci Total Environ. 2022 Aug 5;849:157838. doi: 10.1016/j.scitotenv.2022.157838	Duplicate data for UK Biobank. So Wang 2022 was used as had a larger cohort size
Liu Z, Suo C, Zhao R, Yuan H, Jin L, Zhang T, Chen X. Genetic predisposition, lifestyle risk, and obesity associate with the progression of nonalcoholic fatty liver disease. Dig Liver Dis. 2021 Nov;53(11):1435-1442. doi: 10.1016/j.dld.2021.07.009	Duplicate data for UK Biobank. So Wang 2022 was used as had a larger cohort size
Song Z, Yang R, Wang W, Huang N, Zhuang Z, Han Y, Qi L, Xu M, Tang YD, Huang T. Association of healthy lifestyle including a healthy sleep pattern with incident type 2 diabetes mellitus among individuals with hypertension. Cardiovasc Diabetol. 2021 Dec 18;20(1):239. doi: 10.1186/s12933-021-01434-z	Included sleep and had duplicate data for UK Biobank.
Zhao Y, Li Y, Zhuang Z, Song Z, Wang W, Huang N, Dong X, Xiao W, Jia J, Liu Z, Li D, Huang T. Associations of polysocial risk score, lifestyle and genetic factors with incident type 2 diabetes: a prospective cohort study. Diabetologia. 2022 Jul 21. doi: 10.1007/s00125-022-05761-y	Included sleep and had duplicate data for UK Biobank.

Supplementary table 7. Raw Dose Response Data

Cohort	Paper Dose	Dose	RR	LCI	UCI	Case	Person Years
Australian Diabetes, Obesity and Lifestyle Study (1)	2	2	1	1	1	122	12617
	2.5	2.5	0.75	0.69	0.799	91	12617
	3	3	0.57	0.46	0.695	69	12617
	3.5	3.5	0.43	0.28	0.663	53	12617
	4	4	0.33	0.17	0.639	41	12617
Cardiovascular Health Study (2)	0	0	1.00	1.00	1.00	38	1727
	1	1	0.78	0.55	1.14	105	6217
	2	2	0.58	0.41	0.82	113	8980
	3	3	0.26	0.18	0.40	47	8289
	4	4	0.19	0.11	0.32	24	5871.63
	5	5	0.16	0.11	0.33	10	2763.12
China Kadoorie Biobank Study – Men (3)	0	0	1.00	1.00	1.00	888	188,682
	1	0.83	0.62	0.57	0.68	1212	409,074
	2	1.67	0.34	0.31	0.37	778	448,227
	3	2.5	0.23	0.20	0.26	312	244365
	4	3.33	0.25	0.19	0.32	66	47253
	≥5	4.58	0.19	0.06	0.59	3	2700
China Kadoorie Biobank Study – Women (3)	0	0	1.00	1.00	1.00	121	32537
	1	0.83	0.73	0.60	0.88	2435	518465
	2	1.67	0.40	0.33	0.48	1861	669926
	3	2.50	0.24	0.20	0.29	884	551475
	4	3.33	0.16	0.13	0.21	219	180589
	≥5	4.58	0.19	0.08	0.46	5	5825
Dongfeng-Tongji cohort (4)	0 to 2	0.83	1	1	1	673	24796
	3 or 4	2.92	0.77	0.69	0.87	518	44904

	5 or 6	4.58	0.54	0.45	0.65	364	14146
EPIC-E3N (5)	0 to 2	1	1	1.00	1.00	4596	116334
	2.5 to 3	2.75	0.54	0.46	0.63	20523	369414
	3.5 to 4	3.75	0.31	0.27	0.37	34774	625932
	4.5 to 5	4.75	0.18	0.15	0.22	12762	229716
EPIC-NL (6)	0 or 1	0.5	1	1	1	71	120220
	2	2	0.37	0.22	0.617	61	120220
	3 or 4	3.5	0.26	0.16	0.422	21	120220
EPIC-Norfolk(7)	0	0	1.00	1.00	1.00	74	2516
	1	1	0.69	0.60	0.81	199	9540
	2	2	0.3	0.23	0.37	66	7473
	3 to 5	4	0.24	0.16	0.36	55	4626
EPIC-Potsdam (8)	0	0	1.00	1.00	1.00	148	6510
	1	1	0.34	0.28	0.40	298	42128
	2	2	0.22	0.17	0.27	289	64551
	3	3	0.11	0.10	0.15	113	50990
	4	4	0.07	0.05	0.12	23	16636
Finnish Diabetes Prevention Study (10)	0	0	1.00	1.00	1.00	142	783
	1	0.6	0.86	0.60	1.23	122	783
	2	1.2	0.67	0.45	1.00	95	783
	3	1.8	0.61	0.38	0.98	87	783
	4	2.4	0.34	0.18	0.66	48	783
	5	3	0.20	0.07	0.56	28	783
FINRISK Study – Men (9)	0	0	1.39	0.85	2.11	6000	42582
	1	1	1	1	1	4317	42582
	2	2	0.75	0.62	0.89	3238	42582
	3	3	0.55	0.44	0.66	2374	42582
	4	4	0.53	0.4	0.69	2288	42582

	5	5	0.1	0.05	0.2	432	42582
FINRISK Study – Women (9)	0	0	1.07	0.25	4.51	5541	45763
	1	1	1	1	1	5179	45763
	2	2	0.72	0.48	1.09	3729	45763
	3	3	0.55	0.37	0.81	2848	45763
	4	4	0.4	0.27	0.6	2072	45763
	5	5	0.13	0.08	0.21	673	45763
Health Professionals Follow-up Study (15)	≤2	1	1	1	1	1383	306138.1
	3	3	0.65	0.51	0.82	78	32783.6
	4	4	0.44	0.29	0.64	26	15410.5
	5	5	0.19	0.1	0.38	8	9122.7
Hortega Study (11)	0 or 1	0.5	1.00	1.00	1.00	32	5227
	2	2	0.83	0.44	1.56	17	3458
	3 to 5	4	0.20	0.04	0.88	2	2354
Multiethnic cohort - Men; Caucasian (13)	1	1	1	1	1	364	36184
	Combination of 2	2	0.78	0.38	1.59	283	36184
	Combination of 3	3	0.55	0.33	0.90	199	36184
	Combination of 4	4	0.40	0.21	0.79	147	36184
	Combination of 5	5	0.23	0.19	0.28	85	36184
Multiethnic cohort - Men; Japanese American (13)	1	1	1	1	1	781	40049
	Combination of 2	2	0.97	0.49	1.93	759	40049
	Combination of 3	3	0.70	0.40	1.21	545	40049
	Combination of 4	4	0.48	0.25	0.92	376	40049
	Combination of 5	5	0.26	0.20	0.33	203	40049
Multiethnic cohort - Men; Native Hawaiian (13)	1	1	1	1	1	228	11069
	Combination of 2	2	0.95	0.26	3.51	217	11069
	Combination of 3	3	0.74	0.09	6.49	169	11069
	Combination of 4	4	0.54	0.06	5.00	122	11069

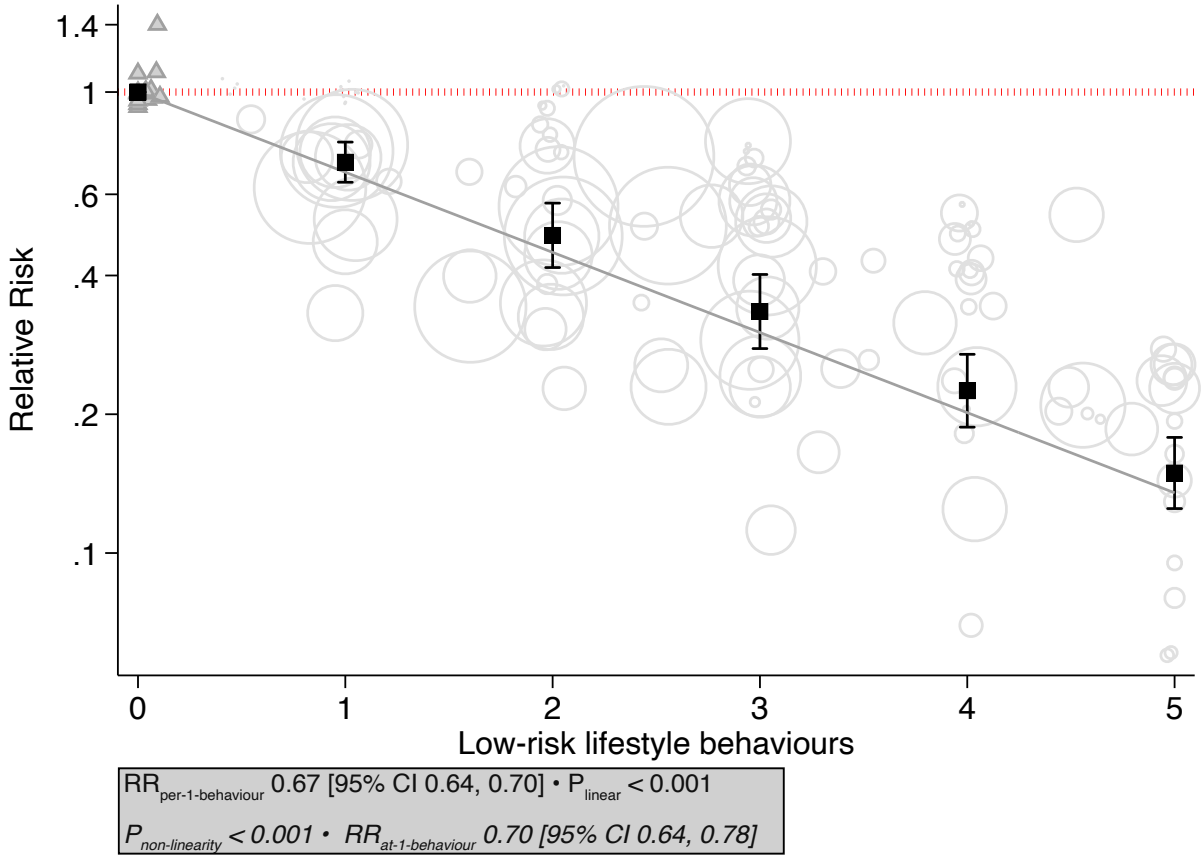
	Combination of 5	5	0.24	0.15	0.39	55	11069
Multiethnic cohort - Women; Caucasian (13)	1	1	1.00	1.00	1.00	238	34742
	Combination of 2	2	0.78	0.38	1.59	185	34742
	Combination of 3	3	0.55	0.33	0.90	130	34742
	Combination of 4	4	0.40	0.21	0.79	96	34742
	Combination of 5	5	0.23	0.19	0.28	55	34742
Multiethnic cohort - Women; Japanese American (13)	1	1	1.00	1.00	1.00	693	45007
	Combination of 2	2	0.97	0.49	1.93	673	45007
	Combination of 3	3	0.70	0.40	1.21	483	45007
	Combination of 4	4	0.48	0.25	0.92	333	45007
	Combination of 5	5	0.26	0.20	0.33	180	45007
Multiethnic cohort - Women; Native Hawaiian (13)	1	1	1.00	1.00	1.00	272	14377
	Combination of 2	2	0.95	0.26	3.51	259	14377
	Combination of 3	3	0.74	0.09	6.49	202	14377
	Combination of 4	4	0.54	0.06	5.00	146	14377
	Combination of 5	5	0.24	0.15	0.39	66	14377
NIH-AARP Diet and Health Study – Men (14)	0	0	1.00	1.00	1.00	860	47220
	1	1	0.75	0.68	0.81	3129	218910
	2	2	0.54	0.50	0.59	3669	345020
	3	3	0.40	0.36	0.44	2433	315370
	4	4	0.24	0.21	0.27	815	177,160
	5	5	0.15	0.1	0.18	125	46,280
NIH-AARP Diet and Health Study – Women (14)	0	0	1	1	1	803	49,490
	1	1	0.73	0.67	0.8	2,578	216,880
	2	2	0.48	0.44	0.52	2,204	277,490
	3	3	0.29	0.27	0.33	1,087	232,290
	4	4	0.13	0.11	0.15	272	127,000
	5	5	0.08	0.04	0.11	25	21,680

Nurses Health Study I (15)	≤2	1	1	1.00	1.00	4367	1152615.89
	3	3	0.58	0.50	0.66	212	31475.2
	4	4	0.48	0.35	0.66	39	7923.3
	5	5	0.06	0.03	0.15	5	5742.6
Nurses Health Study II (15)	≤2	1	1	1	1	3911	1327357.51
	3	3	0.51	0.44	0.58	228	42524.2
	4	4	0.38	0.27	0.52	36	10285.8
	5	5	0.06	0.03	0.14	6	7414
Physicians Health Study I (12)	0	0	1	1	1	313	33109
	1	1	0.70	0.62	0.79	699	107237
	2	2	0.50	0.43	0.56	665	157929
	3	3	0.34	0.28	0.39	321	122763
	4+	4.5	0.24	0.18	0.30	98	51641
Shanghai Men's Health Study (17)	0	0	1	1	1	641	57400.3
	1	1	0.49	0.42	0.57	1422	187575.2
	2	2	0.34	0.29	0.40	1061	201473.8
	3	3	0.23	0.20	0.27	191	72707.6
Shanghai Women's Health Study (17)	0	0	1	1	1	1234	107947.5
	1	1	0.54	0.48	0.61	2590	354334.5
	2	2	0.36	0.32	0.40	1771	382159.0
	3	3	0.24	0.21	0.27	330	137063
Swedish Västerbotten Intervention Programme (19)	0 or 1	0.42	1	1	1	139	11,000
	2	1.66	0.68	0.47	1.02	420	44,500
	3	2.5	0.5	0.35	0.74	612	81,800
	4	3.33	0.4	0.27	0.58	460	84,900
	5	4.17	0.34	0.23	0.49	211	51,000
	6	5	0.27	0.18	0.40	37	12,500
UK Biobank Study (18)	0 or 1	0.5	1	1	1	1193	283271

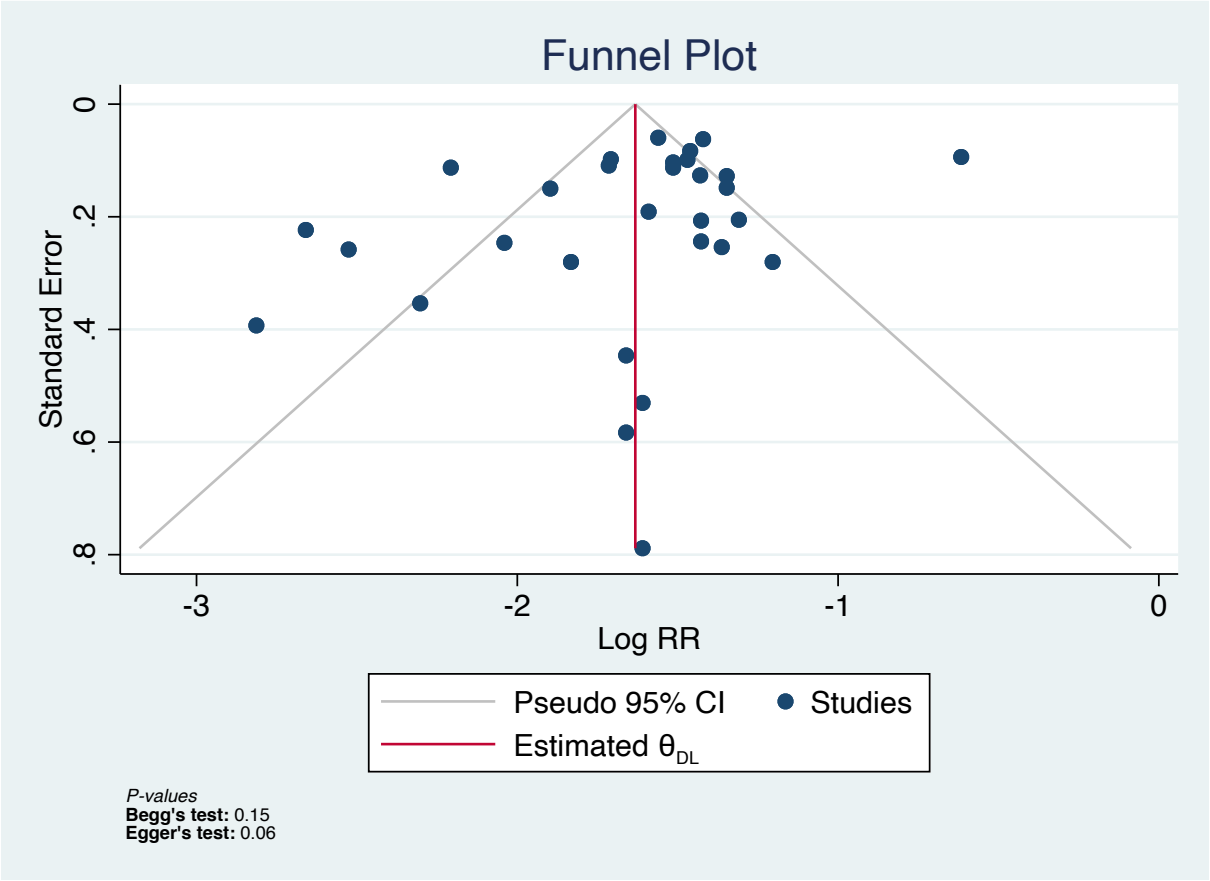
	2 or 3	2.5	0.53	0.49	0.58	3520	1660336.4
	4 or 5	4.5	0.21	0.19	0.24	655	873535.9
Women's Health Study (16)	0	0	1.00	1.00	1.00	415	34307
	1	1	0.77	0.66	0.87	890	113698
	2	2	0.45	0.39	0.52	676	148278
	3	3	0.37	0.30	0.44	320	114491
	4+	4.5	0.20	0.13	0.28	89	51641

Abbreviations: RR=relative risk, LCI=lower confidence interval, UCI=upper confidence interval

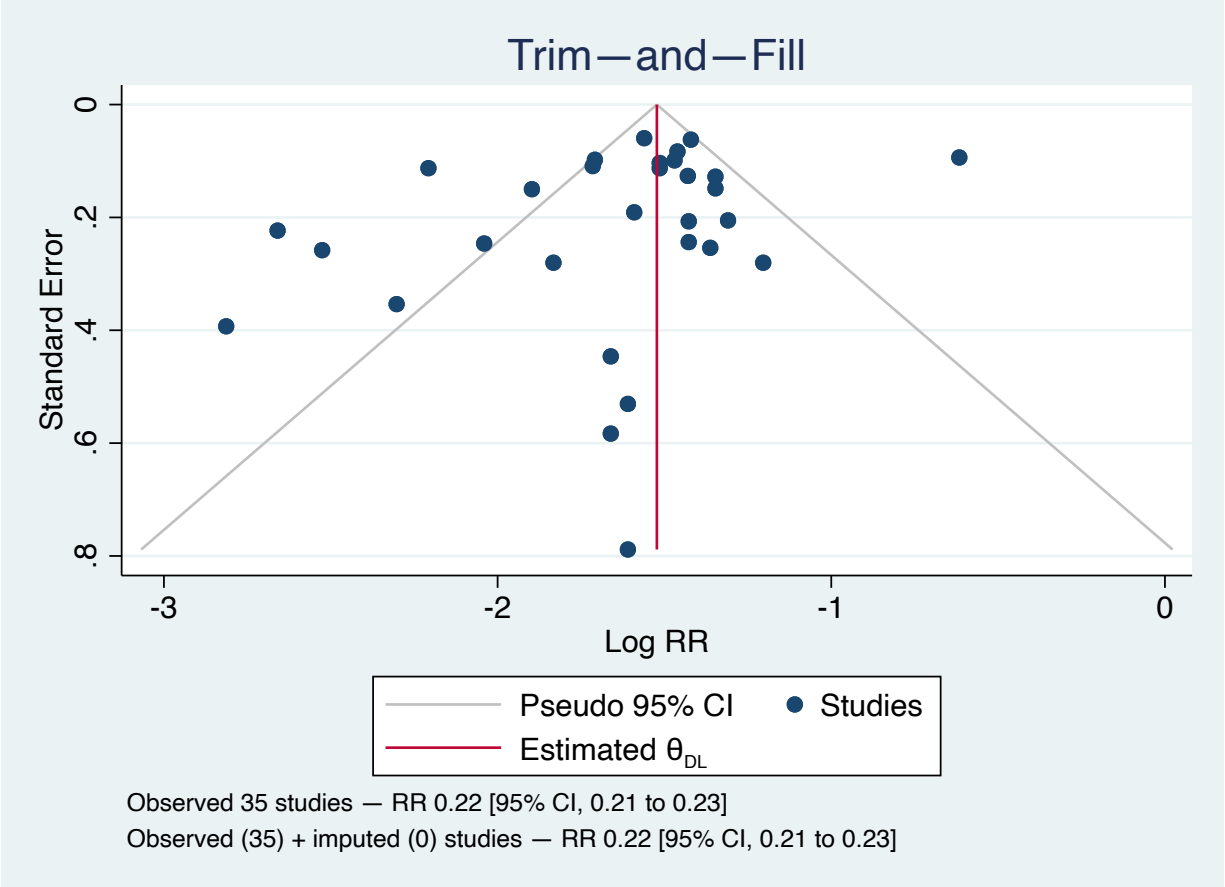
Supplementary figure 1. Dose-response plot of the association of the number of low-risk lifestyle behaviors with incident type 2 diabetes. The grey line represents the relative risks (RRs) for linear dose-response and the black boxes with vertical bars represent the estimated aggregate relative risks (RRs) and 95% CIs for the best-fit non-linear dose-response for each low-risk lifestyle behavior. The light gray circles represent the actual RR point estimates for the different behavior scores from each cohort comparison; the size of the circle is related to the inverse of its variance. The smaller gray triangles with dark gray outline represent the baseline score category for each separate study; a small amount of jitter or random-noise has been added in the graphic display for these gray squares and circles to display overlapping estimates separately. Each additional low risk lifestyle behavior would result in 33% lower risk of type 2 diabetes (RR, 0.67 [95% CI, 0.64 to 0.70]; P_{linear}<0.001). In the non-linear model, compared to adherence to no low-risk lifestyle behaviors, the estimated RRs were 0.70 [95% CI, 0.64 to 0.78] for adherence to one-behavior, 0.49 [95% CI, 0.42 to 0.57] for two-combined behaviors, 0.33 [95% CI, 0.28 to 0.40] for three-combined behaviors, 0.22 [95% CI, 0.19 to 0.27] for four-combined behaviors, and 0.15 [95% CI, 0.12 to 0.18] for all five-combined behaviors [Global DRM]($P_{non-linear}$ <0.001).



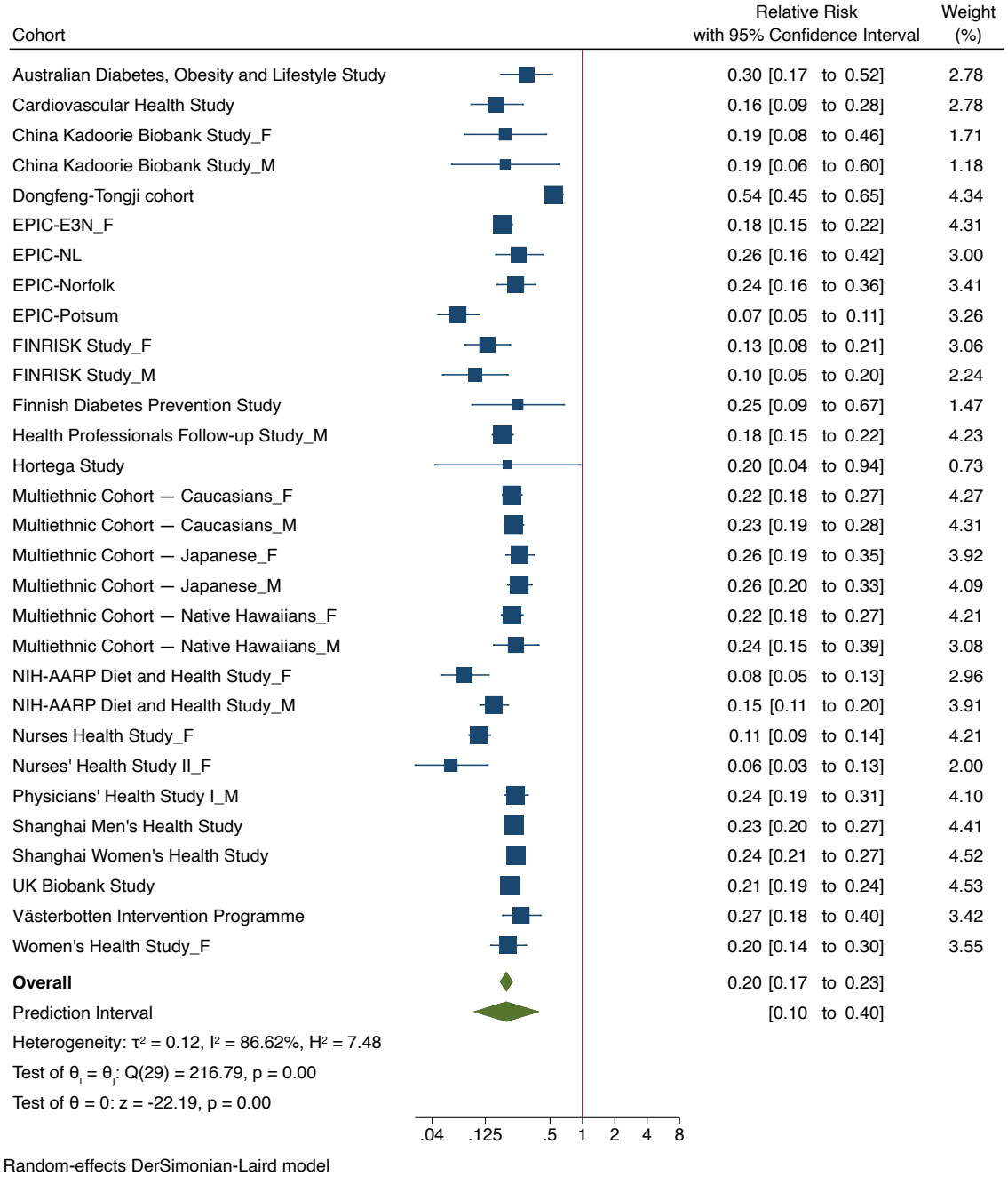
Supplementary figure 2. Funnel plot for publication bias. Begg's funnel plot and Egger's test with the natural log of relative risk (RR) for incident diabetes when comparing extreme comparisons of multiple low-risk lifestyle behaviors. The vertical line represents the pooled estimate. Diagonal lines represent pseudo 95% confidence intervals. Circles represent log RR estimates for individual cohort comparisons.



Supplementary figure 3. Trim-and-fill plot of the log of relative risk (RR) for incident diabetes when comparing extreme comparisons of multiple low-risk lifestyle behaviors. The vertical line represents the pooled estimate. Diagonal lines represent pseudo 95% confidence intervals. Blue dots represent observed estimates of individual cohort comparisons, and orange dotes represent imputed studies using Duval and Tweedie trim-and-fill using right-most run estimator(20).



Supplementary figure 4 – Forest plot of the association of multiple low-risk lifestyle behaviors with type 2 diabetes incidence (highest ≥3 vs. lowest number of behaviors ≤3). The individual study relative risk (RR) estimates are indicated by blue squares, the size proportional to its weight. The blue horizontal lines represent confidence intervals (CIs). Overall pooled estimate is represented by the first green diamond and the prediction interval is represented by the second green diamond. Estimates <1.0 indicate protective association and RR>1.0 indicate an adverse association. Comparison is between highest versus lowest number of low-risk lifestyle behaviors. M=Men; W=Women; N=number of participants; RR=relative risk.



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