SUPPLEMENTARY MATERIAL

Long-term effect of lifestyle interventions in the cardiovascular and all-cause mortality of subjects with prediabetes and type 2 diabetes: A systematic review and meta-analysis

Summary

SUPPLEMENTARY TABLES

Table S1. Search strategy conducted for identifying randomized clinical trials and post-trial follow-up studies of the long-term lifestyle interventions of subjects with prediabetes or type 2 diabetes.

Database	Search terms
PubMed	(Diabetes Mellitus, Type 2[mh] OR Prediabetic State[mh] OR Non-Insulin-Dependent Diabetes Mellitus[tw] OR Type II Diabetes Mellitus[tw] OR Type 2 Diabetes Mellitus[tw] OR Noninsulin-Dependent Diabetes Mellitus[tw] OR Type 2 Diabetes[tw] OR Prediabet*[tw]) **AND** ((“Life Style”[Mesh] OR “Life Style*”[tw] OR Lifestyle*[tw] OR “Healthy Diet*”[tw] OR “Healthy Eating”[tw] OR “Prudent diet*”[tw]) OR (“Weight Loss/diet therapy”[mh] OR Diet Therapy[mh:noexp] OR Diet, Diabetic[mh] OR Dietary Modification*[tw] OR Diet Modification*[tw] OR Diabetic Diet*[tw] OR Weight Reduction Diet*[tw] OR Weight Loss Diet*[tw])) **AND** (((clinical[tiab] AND trial[tiab]) OR clinical trials as topic[mh] OR clinical trial[pt] OR random*[tiab] OR random allocation[mh] OR therapeutic use[sh]) OR (Continuity of Patient Care[mh] OR Follow-Up Studies[mh] OR Continuity of Patient Care[tw] OR Care Continu*[tw] OR Continuum of Care[tw] OR Continuity of Care[tw] OR (care[tw] AND after[tw] AND trial*[tw]) OR post-trial[tw] OR posttrial[tw] OR Follow-Up[tw] OR Followup[tw] OR 24-month*[tw]))
Embase	(“non insulin dependent diabetes mellitus”/exp OR “impaired glucose tolerance”/exp OR “Non-Insulin-Dependent Diabetes Mellitus”:ti,ab,kw OR “Type II Diabetes Mellitus”:ti,ab,kw OR “Type 2 Diabetes Mellitus”:ti,ab,kw OR “Noninsulin-Dependent Diabetes Mellitus”:ti,ab,kw OR “Type 2 Diabetes”:ti,ab,kw OR “Prediabet*”:ti,ab,kw) **AND**(“lifestyle”/exp OR “Life Style*”:ti,ab,kw OR “Lifestyle*”:ti,ab,kw OR “Healthy Diet*”:ti,ab,kw OR “Healthy Eating”:ti,ab,kw OR “Prudent diet*”:ti,ab,kw OR “body weight loss”/exp OR “diet therapy”/de OR “diabetic diet”/exp OR “Dietary Modification*”:ti,ab,kw OR “Diet Modification*”:ti,ab,kw OR “Diabetic Diet*”:ti,ab,kw OR “Weight Reduction Diet*”:ti,ab,kw OR “Weight Loss Diet*”:ti,ab,kw) **AND** (“clinical trial”/exp OR “clinical trial (topic)”/exp OR (“clinical”:ti,ab AND “trial”:ti,ab) OR “random*”:ti,ab OR “randomization”/de OR “drug therapy”/exp OR “patient care”/de OR “patient monitoring”/de OR “follow up”/exp OR “Continuity of Patient Care”:ti,ab,kw OR “Care Continu*”:ti,ab,kw OR “Continuum of Care”:ti,ab,kw OR “Continuity of Care”:ti,ab,kw OR (“care”:ti,ab,kw AND “after”:ti,ab,kw AND “trial*”:ti,ab,kw) OR “post-trial”:ti,ab,kw OR “posttrial”:ti,ab,kw OR “Follow-Up”:ti,ab,kw OR “Followup”:ti,ab,kw OR “24-month*”:ti,ab,kw)
Cochrane	**#1**MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees **#2**MeSH descriptor: [Prediabetic State] explode all trees **#3** "Non-Insulin-Dependent Diabetes Mellitus" **OR** "Type II Diabetes Mellitus" **OR** "Type 2 Diabetes Mellitus" **OR** "Noninsulin-Dependent Diabetes Mellitus" **OR** "Type 2 Diabetes" **OR** Prediabet* **#4** #1 OR #2 OR #3 **#5**MeSH descriptor: [Life Style] explode all trees **#6**MeSH descriptor: [Weight Loss] explode all trees **#7**MeSH descriptor: [Diet Therapy] explode all trees **#8**MeSH descriptor: [Diet, Diabetic] explode all trees **#9** "Life Style*" **OR** Lifestyle* **OR** "Healthy Diet*" **OR** "Healthy Eating" **OR** "Prudent diet*" **OR** "Dietary Modification*" **OR** "Diet Modification*" **OR** "Diabetic Diet*" **OR** "Weight Reduction Diet*" **OR** "Weight Loss Diet*" **#10** #5 OR #6 OR #7 OR #8 OR #9 **#11**MeSH descriptor: [Clinical Trials as Topic] explode all trees **#12**MeSH descriptor: [Clinical Trial] explode all trees **#13**MeSH descriptor: [Random Allocation] explode all trees **#14**MeSH descriptor: [Follow-Up Studies] explode all trees **#15** (clinical AND trial) **OR** random* **OR** "Continuity of Patient Care" **OR** "Care Continu*" **OR** "Continuum of Care" **OR** "Continuity of Care" **OR** (care AND after AND trial*) **OR** "post-trial" **OR** posttrial **OR** "Follow-Up" **OR** Followup**OR**"24-month*" **#16** #11 OR #12 OR #13 OR #14 OR #15 **#17** #4 AND #10 AND #16
Web of Science	ALL=((“Non-Insulin-Dependent Diabetes Mellitus” OR “Type II Diabetes Mellitus” OR “Type 2 Diabetes Mellitus” OR “Noninsulin-Dependent Diabetes Mellitus” OR “Type 2 Diabetes” OR Prediabet*) **AND** (“Life Style*” OR Lifestyle* OR “Healthy Diet*” OR “Healthy Eating” OR “Prudent diet*” OR “Dietary Modification*” OR “Diet Modification*” OR “Diabetic Diet*” OR “Weight Reduction Diet*” OR “Weight Loss Diet*”) **AND** ((clinical AND trial) OR random* OR “Continuity of Patient Care” OR “Care Continu*” OR “Continuum of Care” OR “Continuity of Care” OR (care AND after AND trial*) OR “post-trial” OR posttrial OR “Follow-Up” OR Followup OR “24-month*”))

Table S2. Reasons for exclusion in the selection and extraction of records.
Initial search: 31,399

	Search	Title and abstract	Full text	Data extraction	Analysis
Duplicates	7,830	234	0	0	-
Study design	-	16,534	35	33	-
Population	-	1,286	40	10	-
Type of intervention	-	3,372	48	21	-
Length of intervention	-	1,569	28	2	-
Outcomes	-	84	21	17	-
No access to full-text	-	-	5	-	-
Conference abstracts and study records	-	-	188	-	-
No access to data	-	-	-	3	-
Results of the same study with shorter follow-up time	-	-	-	-	28
Total	23,569	490	125	39	11

Table S3. Quality and certainty of evidence of included studies through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Certainty assessment							Summary of findings				
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With lifestyle interventions		Risk with control	Risk difference with lifestyle interventions
All-cause mortality (follow-up: mean 11 years)											
16554 (11 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	1085/7772 (14.0%)	1205/8782 (13.7%)	RR 0.93 (0.85 to 1.03)	140 per 1.000	**10 fewer per 1,000** (From 21 fewer to 4 more)
Cardiovascular mortality (follow-up: median 15.8 years)											
11017 (5 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	274/5213 (5.3%)	353/5804 (6.1%)	RR 0.99 (0.79 to 1.23)	53 per 1.000	**1 fewer per 1,000** (From 11 fewer to 12 more)

CI, confidence interval; RR, relative risk

Explanations

[a] Confidence interval includes important benefit and harm.

Table S4. Results of Meta Analysis, Subgroup and Sensitivity analyses according to Der Simonian and Laird and Generalized Linear Mixed Model methods.

Analysis	DerSimonian and Laird	Generalized Linear Mixed Model
Principal Results		
Meta-analysis of the effect of intensive lifestyle interventions and all-cause mortality	RR, 0.93; 95% CI, 0.85 to 1.03	RR, 0.95; 95% CI, 0.87 to 1.03
Meta-analysis of the effect of intensive lifestyle interventions and cardiovascular mortality	RR, 0.99; 95% CI, 0.79 to 1.23	RR, 1.01; 95% CI, 0.86 to 1.18
Sensitivity and Subgroup Analysis – All cause mortality		
Sensitivity analysis of the effect of intensive lifestyle interventions on all-cause mortality excluding studies that reported mortality as loss to follow-up	RR, 0.92; 95% CI, 0.82 to 1.04	Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the glycemic status of the study population	Prediabetes RR, 0.91; 95% CI, 0.70 to 1.18 Diabetes RR, 0.94; 95% CI, 0.87 to 1.03	Prediabetes RR, 1.08; 95% CI, 0.87 to 1.35 Diabetes RR, 0.92; 95% CI, 0.84 to 1.01
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the geographic area of the studies	Europe RR, 0.91; 95% CI, 0.77 to 1.07 Asia RR, 0.98; 95% CI, 0.62 to 1.55 North America RR, 0.99; 95% CI, 0.84 to 1.16	Europe RR, 0.91; 95% CI, 0.76 to 1.09 Asia RR, 0.96; 95% CI, 0.68 to 1.35 North America Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality by the mean age of participants (adults or elderly)	Less than 60 years old RR, 0.95; 95% CI, 0.82 to 1.09 Equal or more than 60 years old RR, 0.92; 95% CI, 0.78 to 1.09	Less than 60 years old RR, 0.95; 95% CI, 0.87 to 1.05 Equal or more than 60 years old RR, 0.93; 95% CI, 0.77 to 1.11
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the dietary intervention modality of the studies	Dietary prescription RR, 0.91; 95% CI, 0.79 to 1.05 Group based activities RR, 0.97; 95% CI, 0.83 to 1.13	Dietary prescription RR, 0.93; 95% CI, 0.85 to 1.03 Group based activities RR, 0.98; 95% CI, 0.83 to 1.16

Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the physical exercise intervention modality of the studies	Exercise prescription RR, 0.91; 95% CI, 0.79 to 1.05 General recommendation RR, 0.97; 95% CI, 0.83 to 1.13	Exercise prescription RR, 0.94; 95% CI, 0.85 to 1.03 General recommendation RR, 0.97; 95% CI, 0.83 to 1.15
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the mean follow-up of the studies	Less than 11 years RR, 0.97; 95% CI, 0.83 to 1.13 Equal or more than 11 years RR, 0.91; 95% CI, 0.77 to 1.08	Less than 11 years RR, 0.98; 95% CI, 0.83 to 1.15 Equal or more than 11 years RR, 0.96; 95% CI, 0.87 to 1.07
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the risk of bias of the studies	Some concerns RR, 0.82; 95% CI, 0.39 to 1.74 Low risk RR, 0.94; 95% CI, 0.83 to 1.06	Some concerns RR, 0.84; 95% CI, 0.39 to 1.80 Low risk RR, 0.95; 95% CI, 0.87 to 1.03
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to the control group of the studies	No advice at all about diet and exercise RR, 0.77; 95% CI, 0.64 to 0.93 Usual care according to each center RR, 1.00; 95% CI, 0.79 to 1.25 General information, some degree of intervention RR, 0.96; 95% CI, 0.88 to 1.05	No advice at all about diet and exercise RR, 0.78; 95% CI, 0.60 to 1.02 Usual care according to each center RR, 0.97; 95% CI, 0.82 to 1.14 General information, some degree of intervention RR, 0.97; 95% CI, 0.82 to 1.14
Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality according to intervention dilution over time	2 to 5 years RR, 1.10; 95% CI, 0.38 to 3.18 6 to 15 years RR, 0.92; 95% CI, 0.82 to 1.04 16 to 30 years RR, 0.92; 95% CI, 0.77 to 1.10	Not applicable*
Sensitivity and Subgroup Analysis – Cardiovascular Mortality		
Sensitivity analysis of the effect of intensive lifestyle interventions on cardiovascular mortality excluding studies that reported cardiovascular mortality as losses to follow-up	RR, 0.98; 95% CI, 0.78 to 1.24	Not applicable*
Sensitivity analysis including only studies with low risk of bias in the overall classification.		
Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the glycemic status of the study population	Prediabetes RR, 0,97; 95% CI, 0.55 to 1.72 Diabetes RR, 1.04; 95% CI, 0.86 to 1.25	Prediabetes RR, 1.32; 95% CI, 0.87 to 2.01 Diabetes Not applicable*

Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality by the mean age of participants (adults or elderly)	Less than 60 years old RR, 0.98; 95% CI, 0.72 to 1.32 Equal or more than 60 years old RR, 1.05; 95% CI, 0.72 to 1.53	Less than 60 years old RR, 0.99; 95% CI, 0.80 to 1.23 Equal or more than 60 years old Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the dietary intervention modality of the studies Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the physical exercise intervention modality of the studies	Dietary prescription RR, 0.98; 95% CI, 0.72 to 1.32 Group based activities RR, 1.05; 95% CI, 0.72 to 1.53 Exercise prescription RR, 0.98; 95% CI, 0.72 to 1.32 General recommendation RR, 1.05; 95% CI, 0.72 to 1.53	Dietary prescription RR, 0.99; 95% CI, 0.80 to 1.23 Group based activities Not applicable* Exercise prescription RR, 0.99; 95% CI, 0.80 to 1.23 General recommendation Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the mean follow-up of the studies	Less than 15.8 years RR, 1.04; 95% CI, 0.86 to 1.26 Equal or more than 15.8 years RR, 0.94; 95% CI, 0.51 to 1.72	Less than 15.8 years RR, 1.04; 95% CI, 0.86 to 1.27 Equal or more than 15.8 years Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the geographic area of the studies	Europe RR, 1.06; 95% CI, 0.73 to 1.54 Asia RR, 1.70; 95% CI, 0.51 to 0.97 North America RR, 1.09; 95% CI, 0.90 to 1.32	Europe RR, 1.07; 95% CI, 0.73 to 1.56 Asia Not applicable* North America Not applicable*
Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the control group of the studies	No advice at all about diet and exercise RR, 0.71; 95% CI, 0.52 to 0.98 Usual care according to each center RR, 1.05; 95% CI, 0.72 to 1.53 General information, some degree of intervention RR, 1.09; 95% CI, 0.90 to 1.32	No advice at all about diet and exercise RR, 0.72; 95% CI, 0.49 to 1.04 Usual care according to each center Not applicable* General information, some degree of intervention Not applicable*

RR, relative risk

*Not Applicable: Analysis that did not include studies with low or zero events.

Table S5. PRISMA Check-list.

Section and Topic	Item #	Checklist item	Location where item is reported
Long-term effect of lifestyle interventions in mortality of subjects with prediabetes and type 2 diabetes: A systematic review and meta-analysis			
Title	1	Identify the report as a systematic review.	Pg 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 6, 7 and Fig.1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg 8, 9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 8, 9,10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 8, 9,10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg 9, 10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg 9, 10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg 10

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg 9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Table S2 and Fig.1
Study characteristics	17	Cite each included study and present its characteristics.	Pg 10, 11,12
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pg 13, Figures S1, S2
Result of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2 and 3, pages 13 and 14
Result of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pg 13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the Direction of the effect.	Pg 13, 14,15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pg 13, 14,15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg 13, 14
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pg 13, 14, Table S3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 15, 16
	23b	Discuss any limitations of the evidence included in the review.	Pg. 16,17
	23c	Discuss any limitations of the review processes used.	Pg 18, 19
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 4, 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	20
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg 4, 21
Competing interests	26	Declare any competing interests of review authors.	Pg 21
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

SUPPLEMENTARY FIGURES

Figure S1. Risk of bias of studies that tested the effect of intensive lifestyle interventions on all-cause mortality using the RoB 2.0 tool.

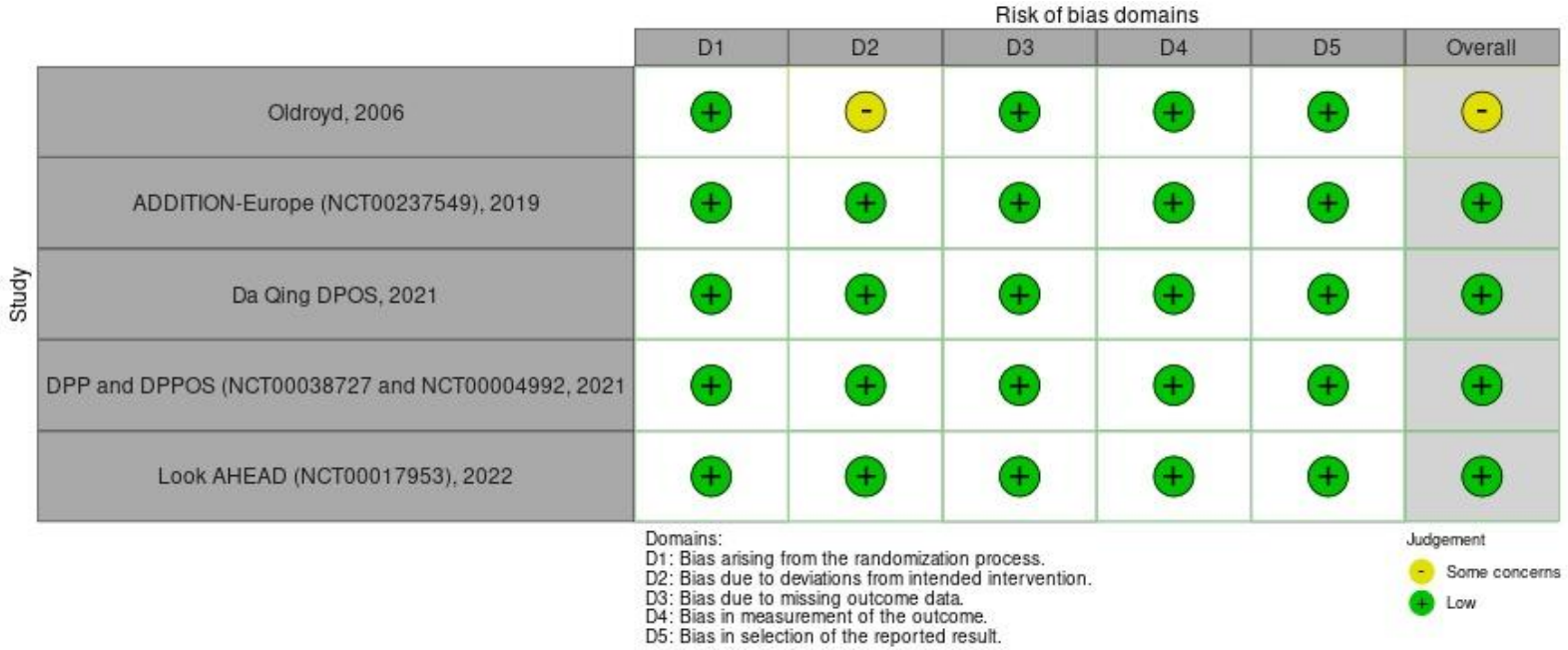


Figure S2. Risk of bias of studies that tested the effect of intensive lifestyle interventions on cardiovascular mortality using the RoB 2.0 tool.

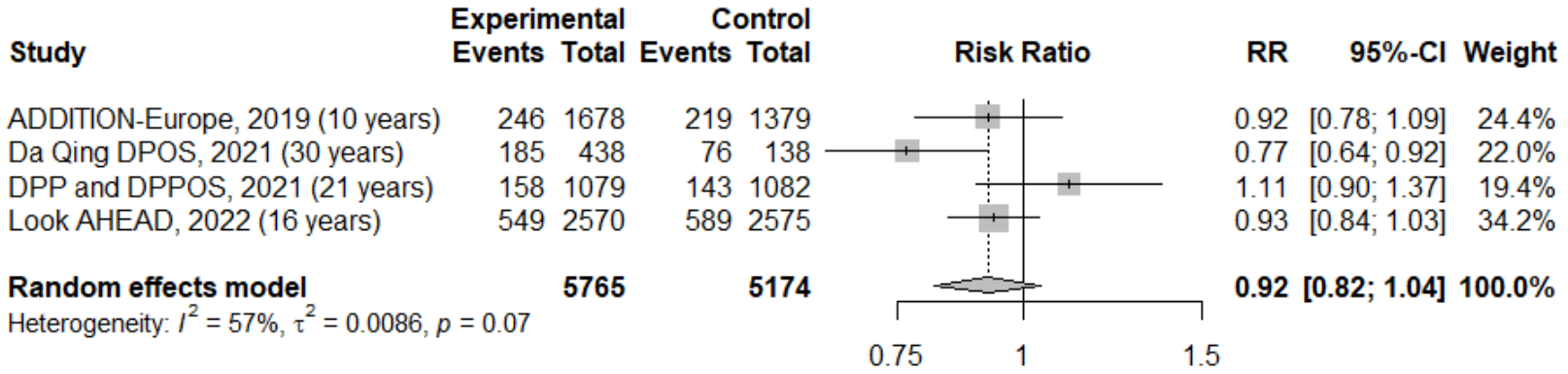


Figure S3. Sensitivity analysis to assess the effect of intensive lifestyle interventions on all-cause mortality excluding studies that reported mortality as losses to follow-up.

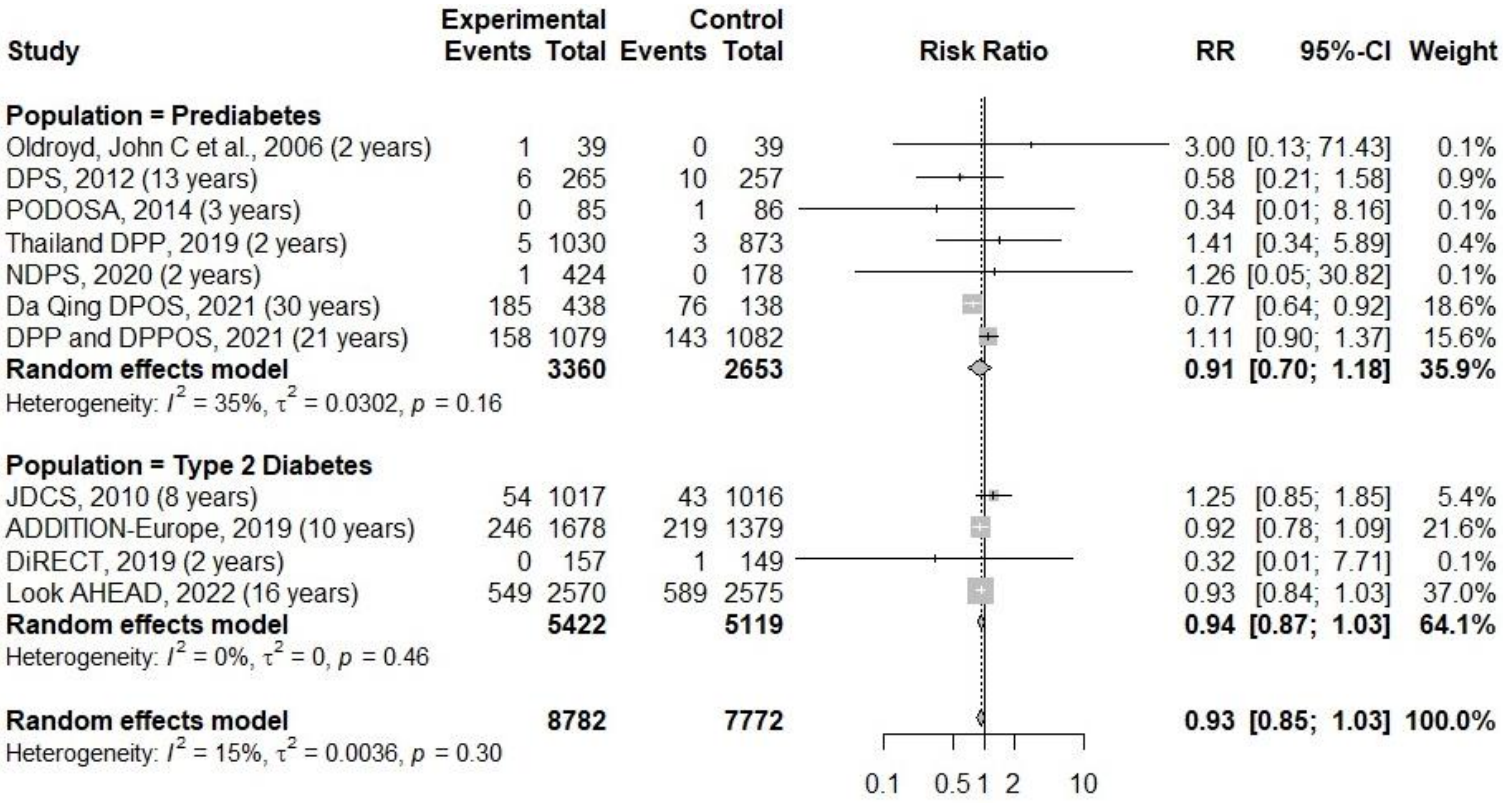


Figure S4. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the glycemic status of the study population.

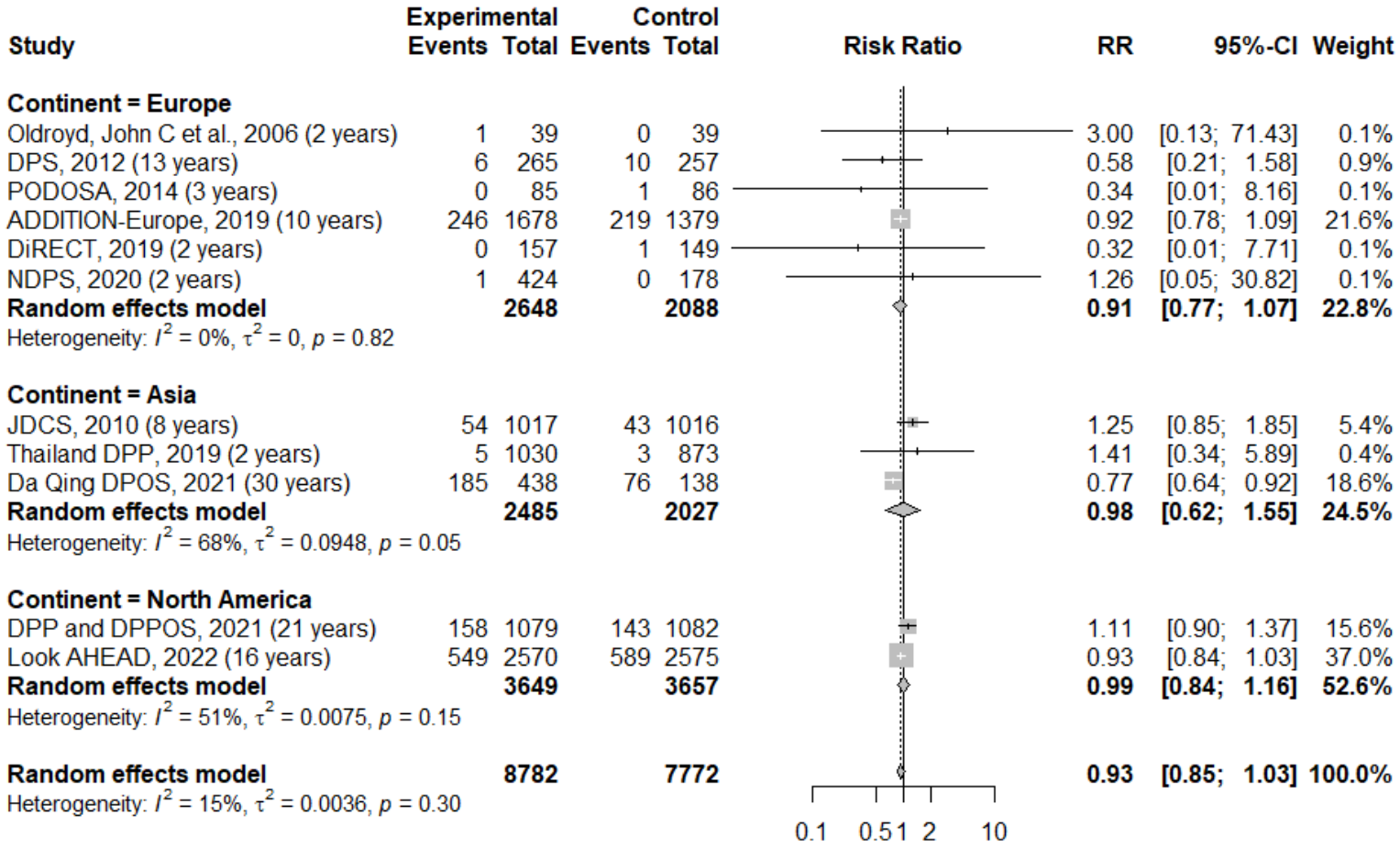


Figure S5. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the geographic area of the studies.

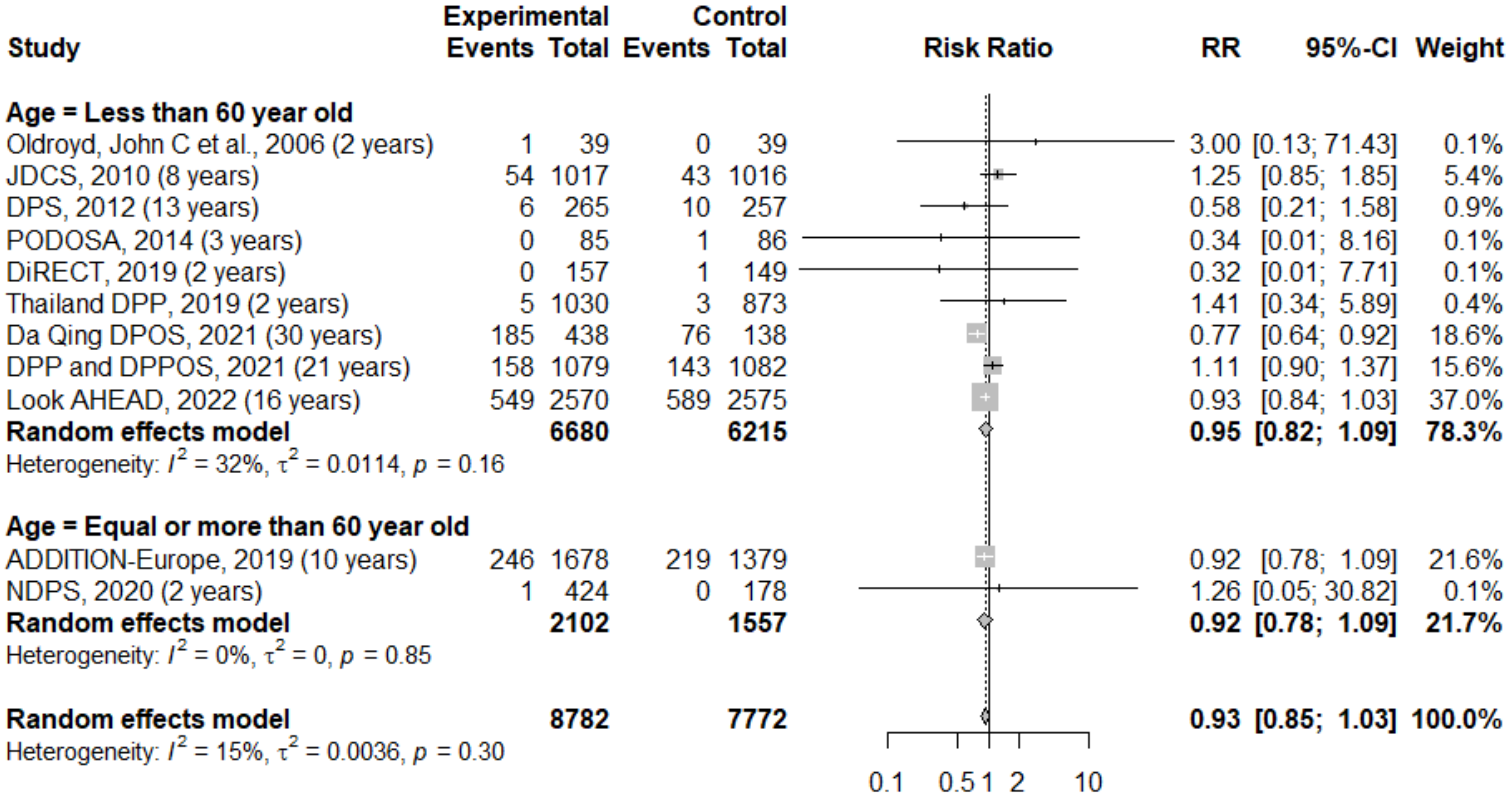
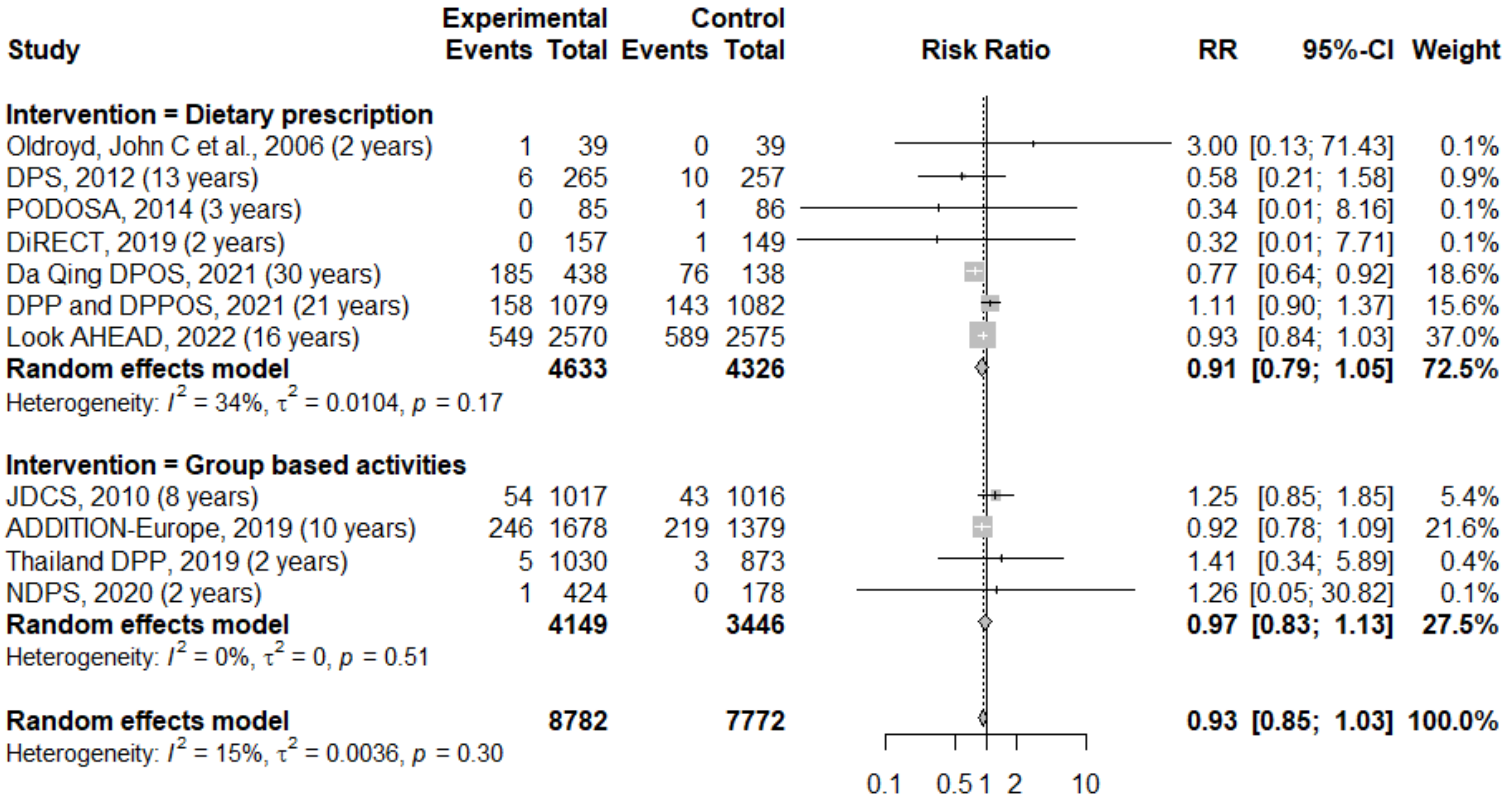


Figure S6. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model by the mean age of participants (adults or elderly, according to the cutoff of 60 years-old).



Studies were considered as “dietary prescription” if they had individual counseling or caloric and nutrient targets as part of intervention groups.

Figure S7. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the dietary intervention modality of the studies.

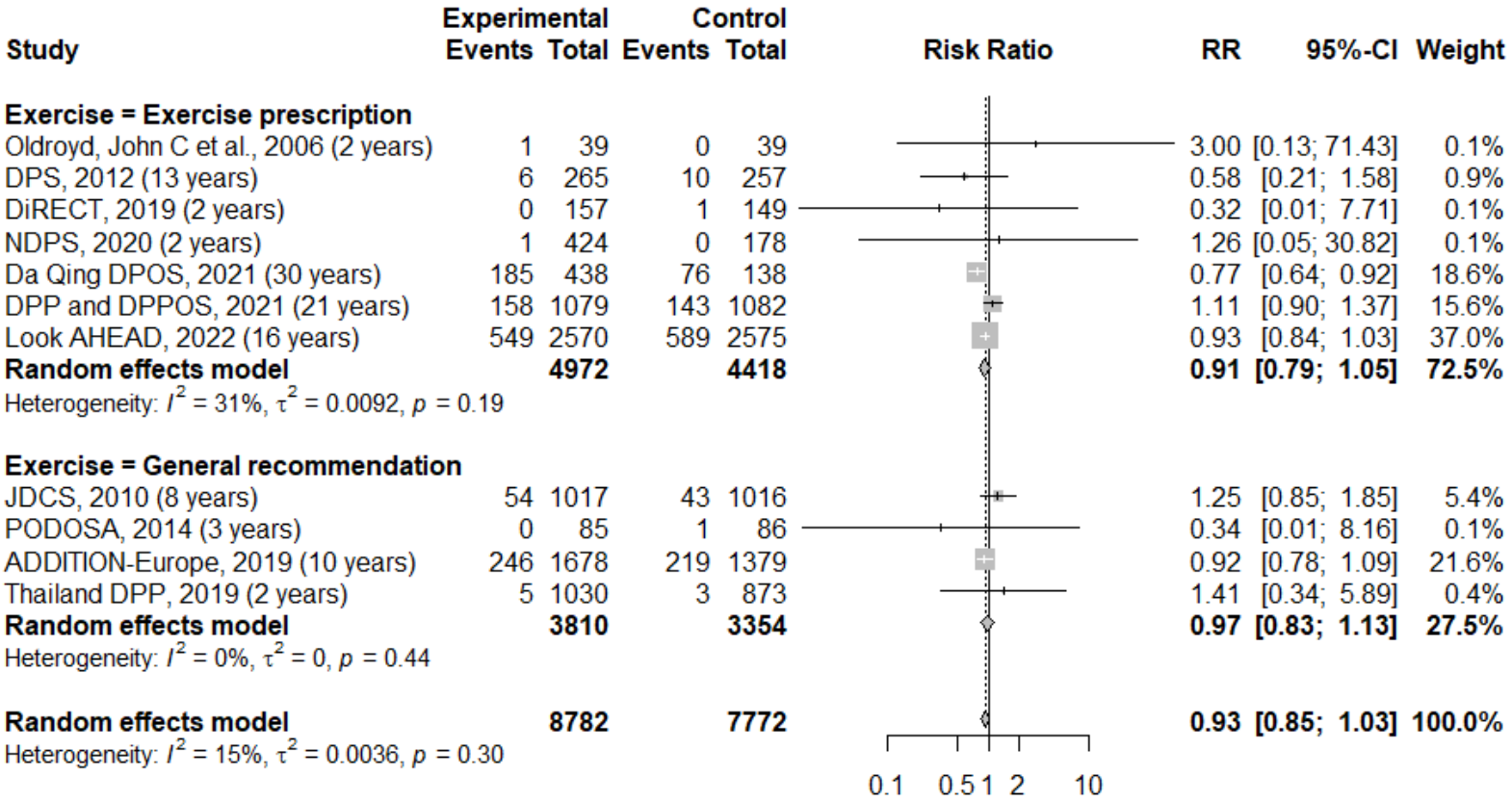


Figure S8. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the physical exercise intervention modality of the studies.

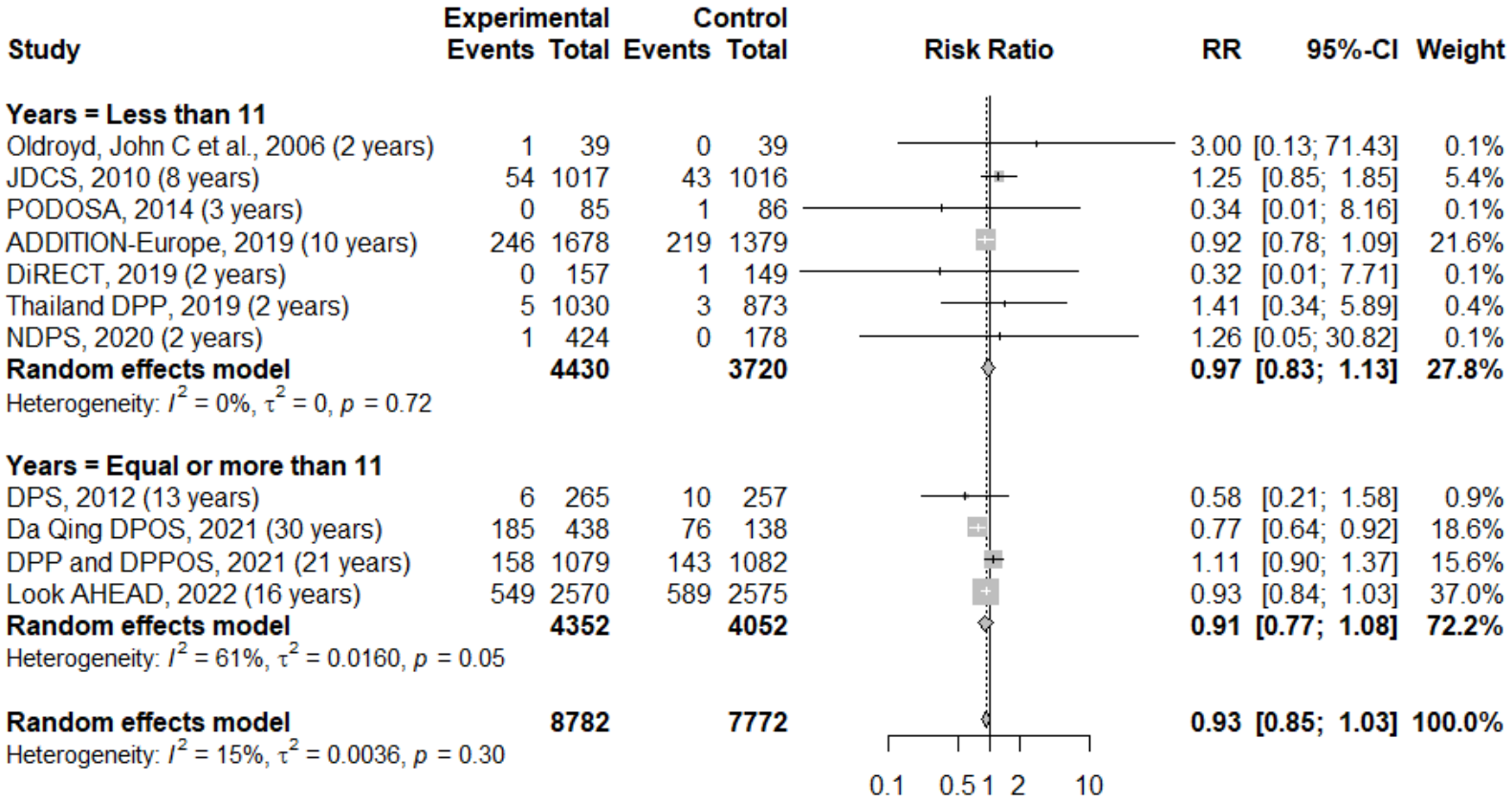


Figure S9. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the mean follow-up of the studies.

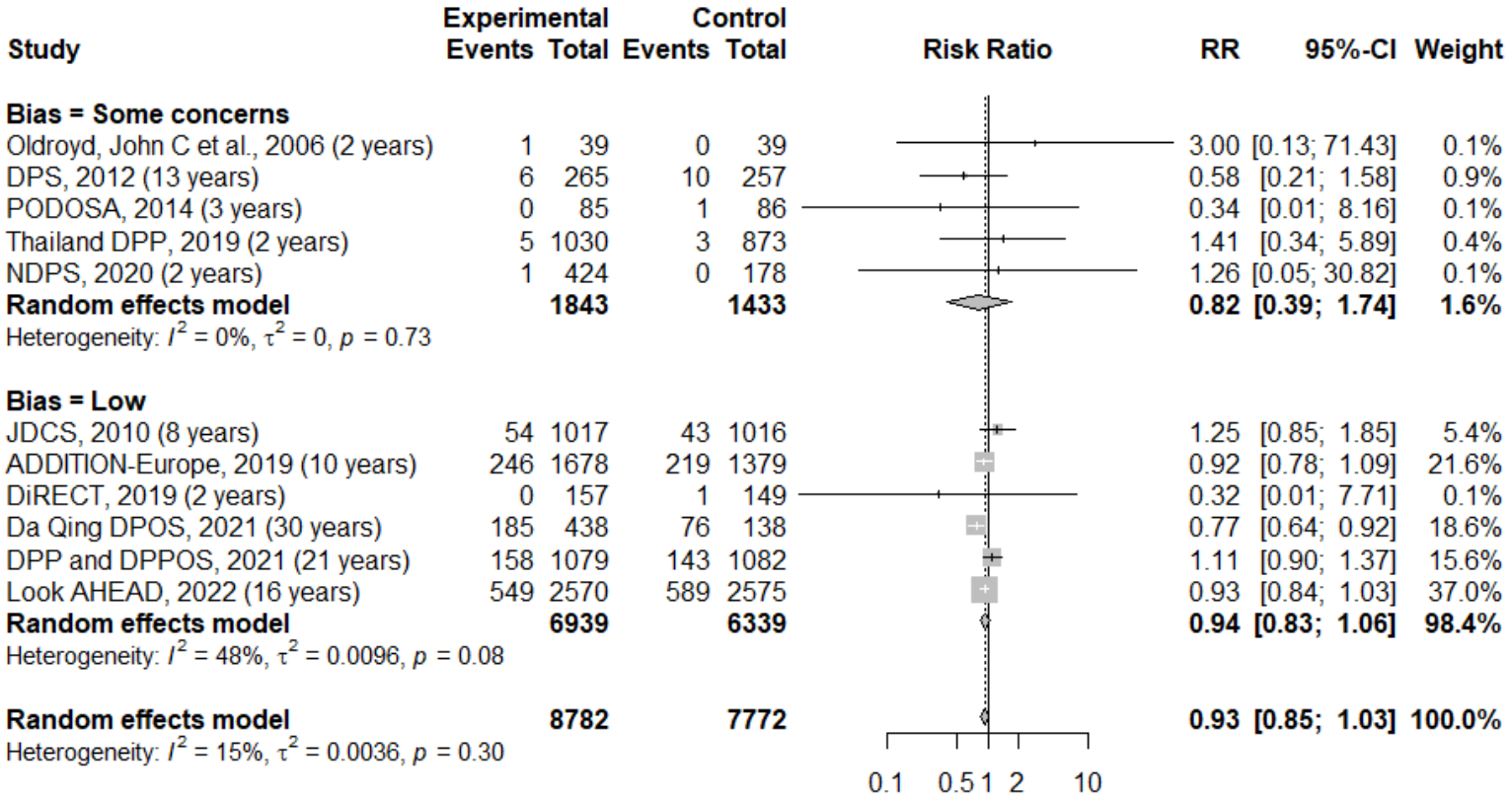


Figure S10. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the risk of bias of the studies.

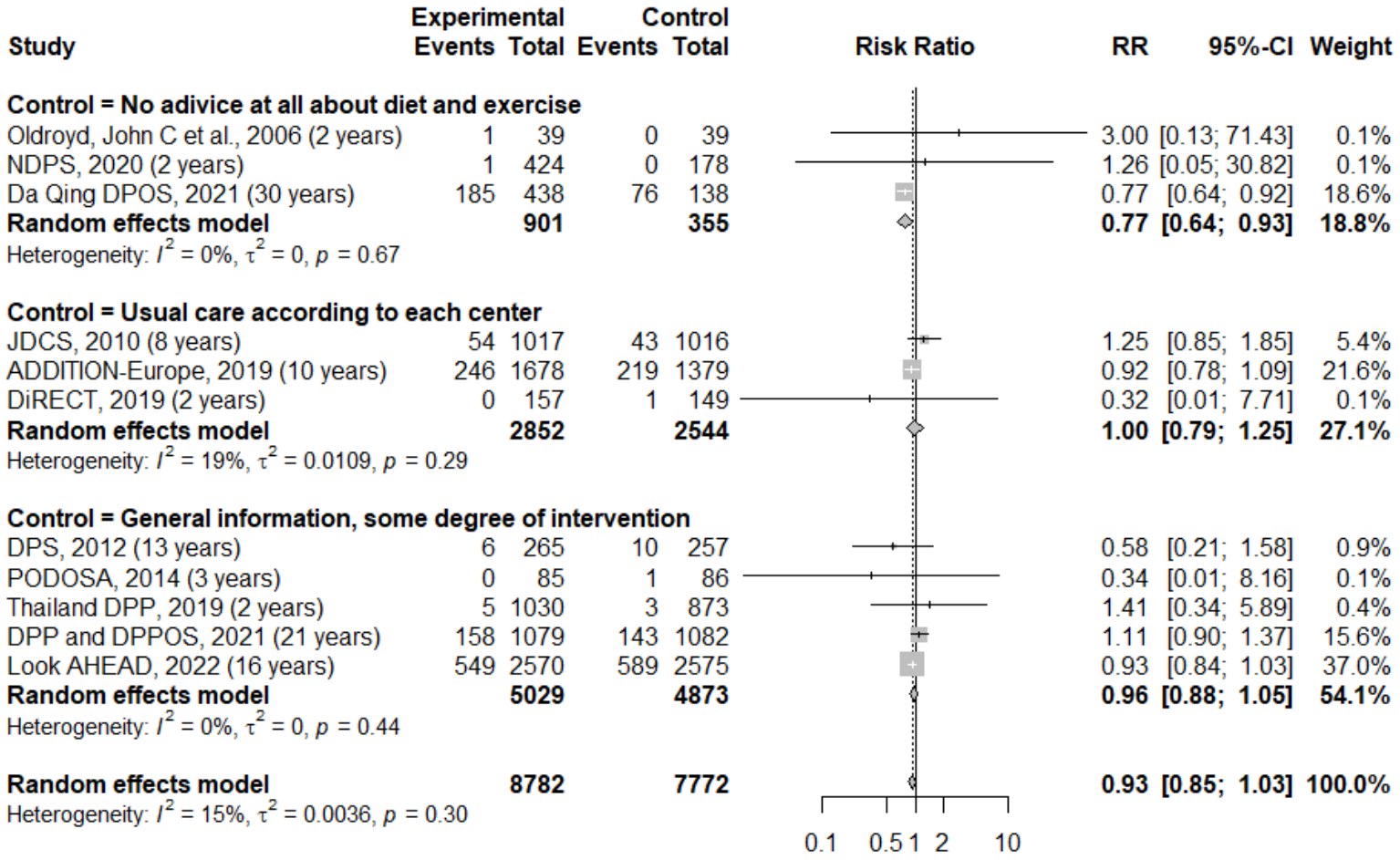
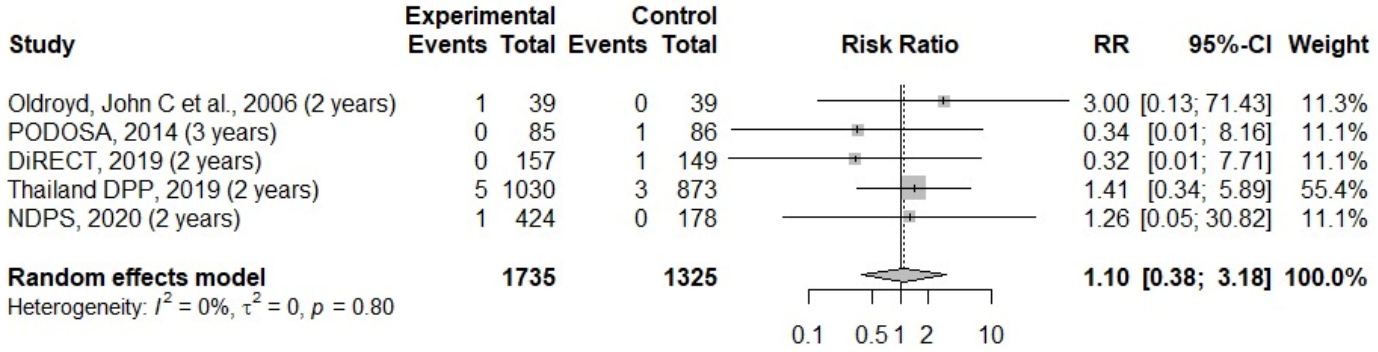
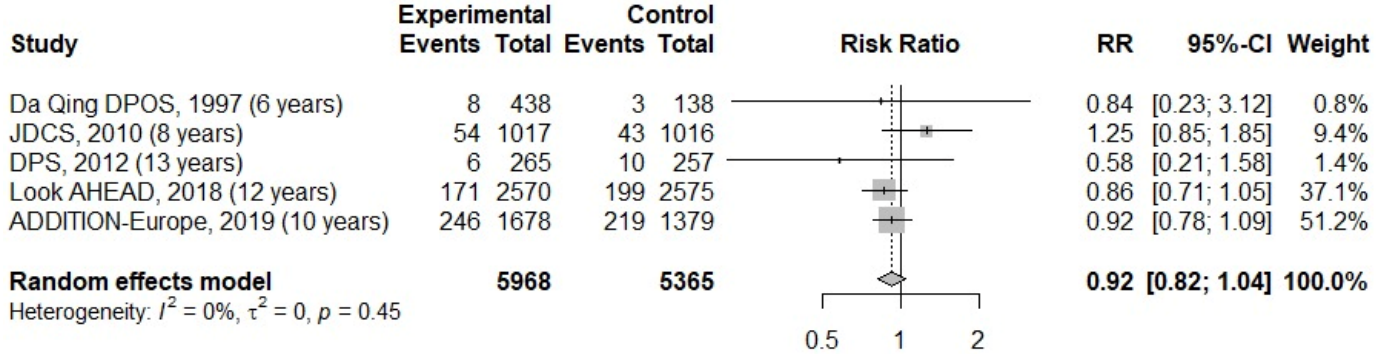


Figure S11. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to the characteristics of control groups of the studies.

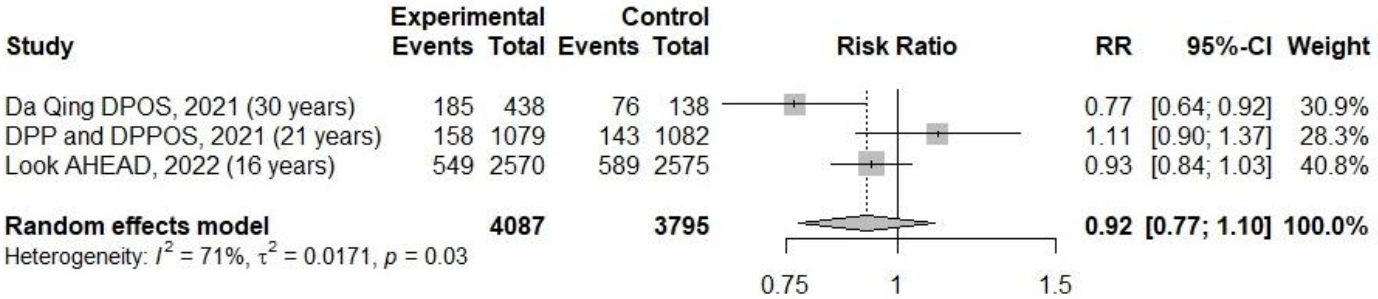
(A)



(B)

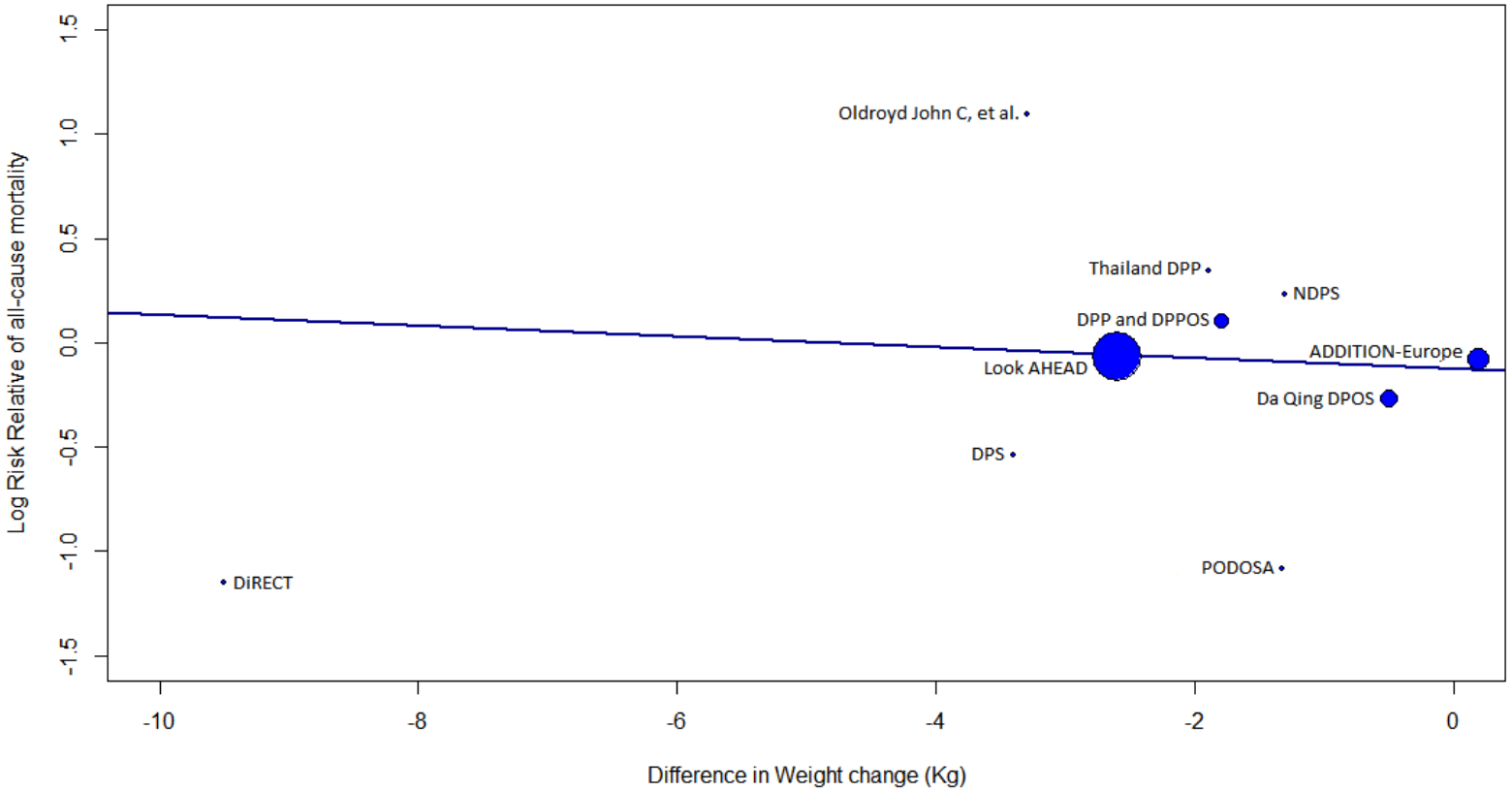


(C)



(A) Studies with follow-up between 2 and 5 years; (B) Studies with follow-up between 6 and 15 years; (C) Studies with follow-up between 16 and 30 years

Figure S12. Subgroup analysis of the effect of intensive lifestyle interventions on all-cause mortality using a random-effect model according to intervention dilution over time.



DPS, Finnish Diabetes Prevention Study; PODOSA, Prevention of Diabetes and Obesity in South Asians; Look AHEAD, Look Action for Health in Diabetes; Thailand DPP, Community-Based Diabetes Prevention Program in Thailand; ADDITION-EUROPE, Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care; Da Qing DPOS, China Da Qing Diabetes Prevention Outcomes Study; DiRECT, Diabetes Remission Clinical Trial; NDPS, Norfolk Diabetes Prevention Study; DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study.

Figure S13. Meta regression of the relationship between mean weight change (intervention - control) and relative risk of all-cause mortality.

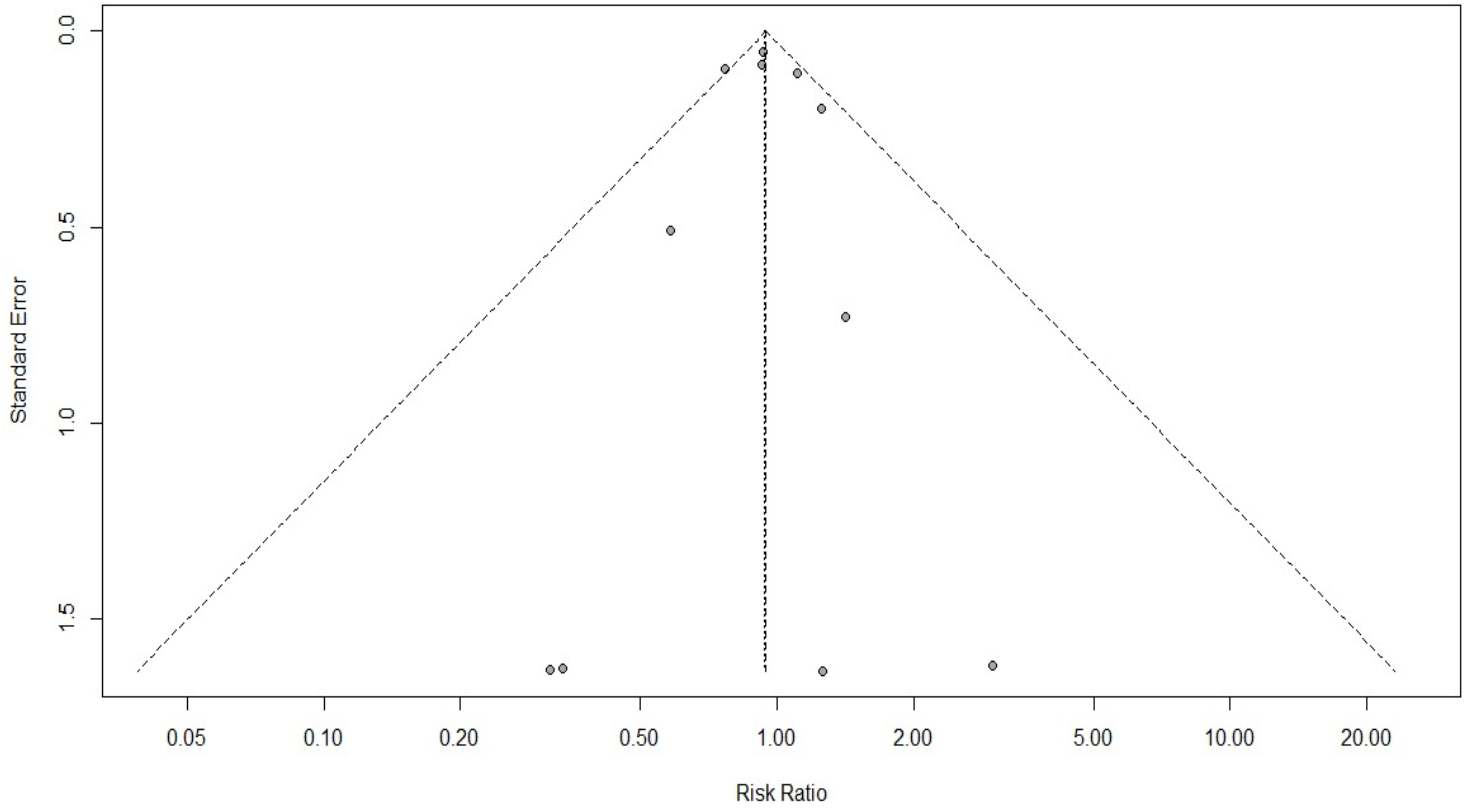


Figure S14. Funnel plot of studies that tested the effect of intensive lifestyle interventions on all-cause mortality.

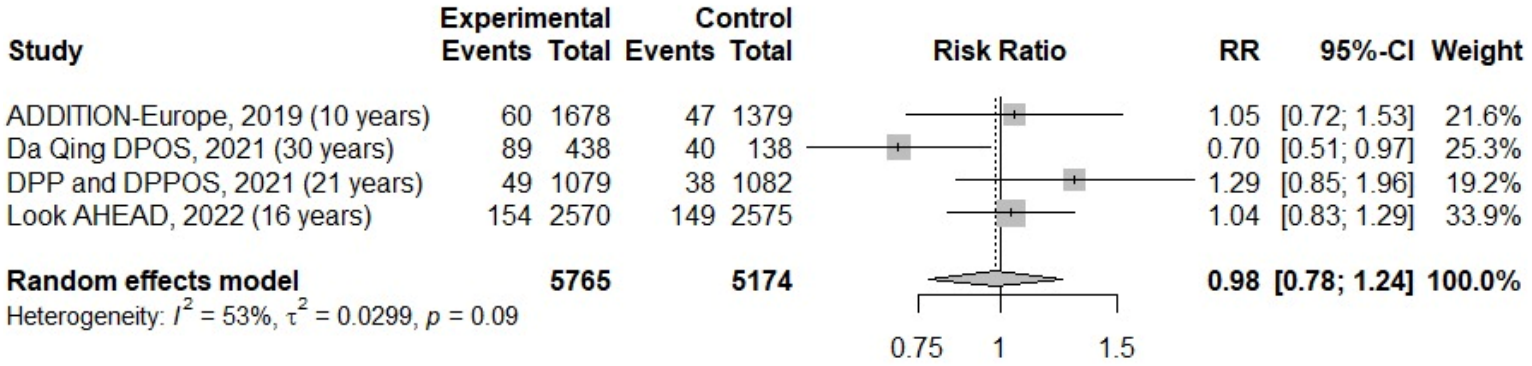


Figure S15. Sensitivity analysis of the effect of intensive lifestyle interventions on cardiovascular mortality excluding studies that reported cardiovascular mortality as loss to follow-up.

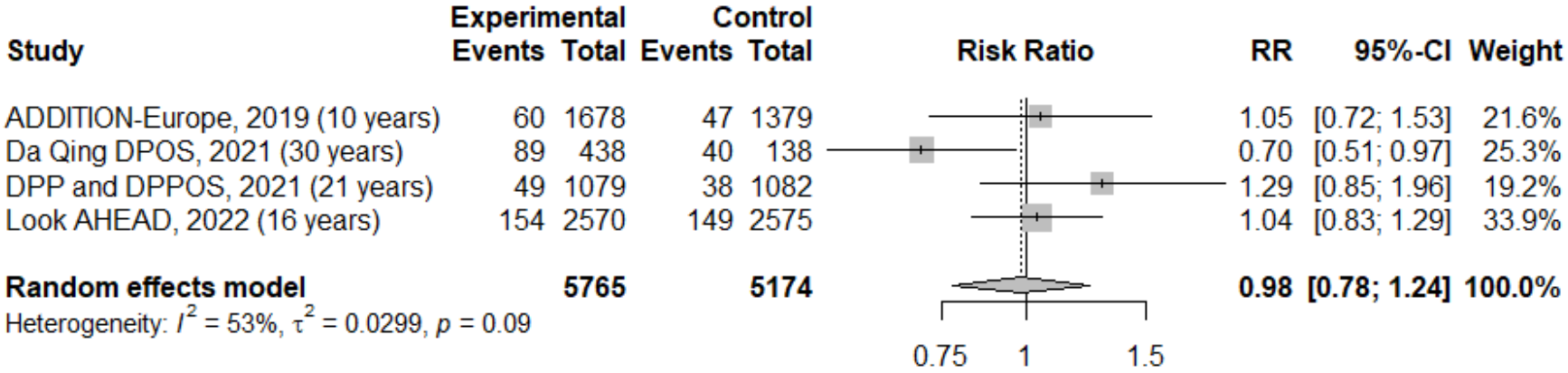


Figure S16. Sensitivity analysis of the effect of intensive lifestyle interventions on cardiovascular mortality excluding the study with some concerns in the risk of bias.

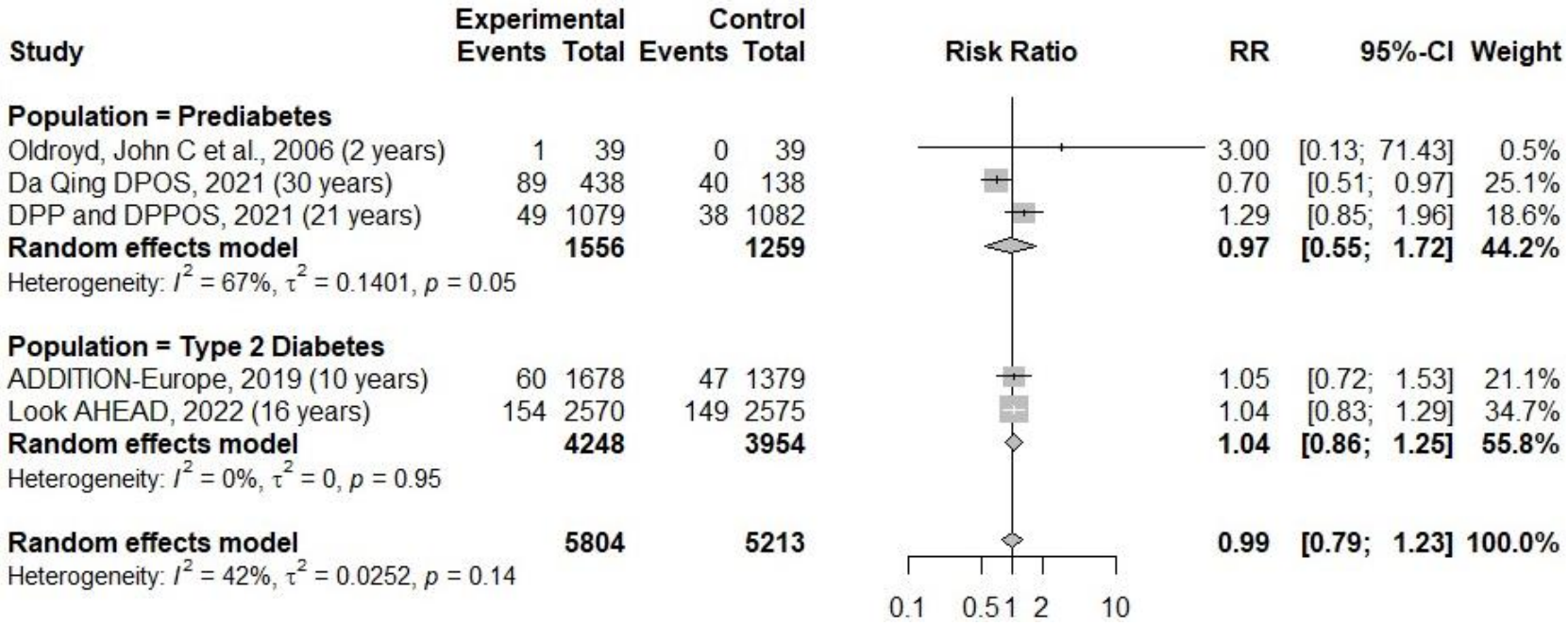


Figure S17. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the glycemic status of the study population.

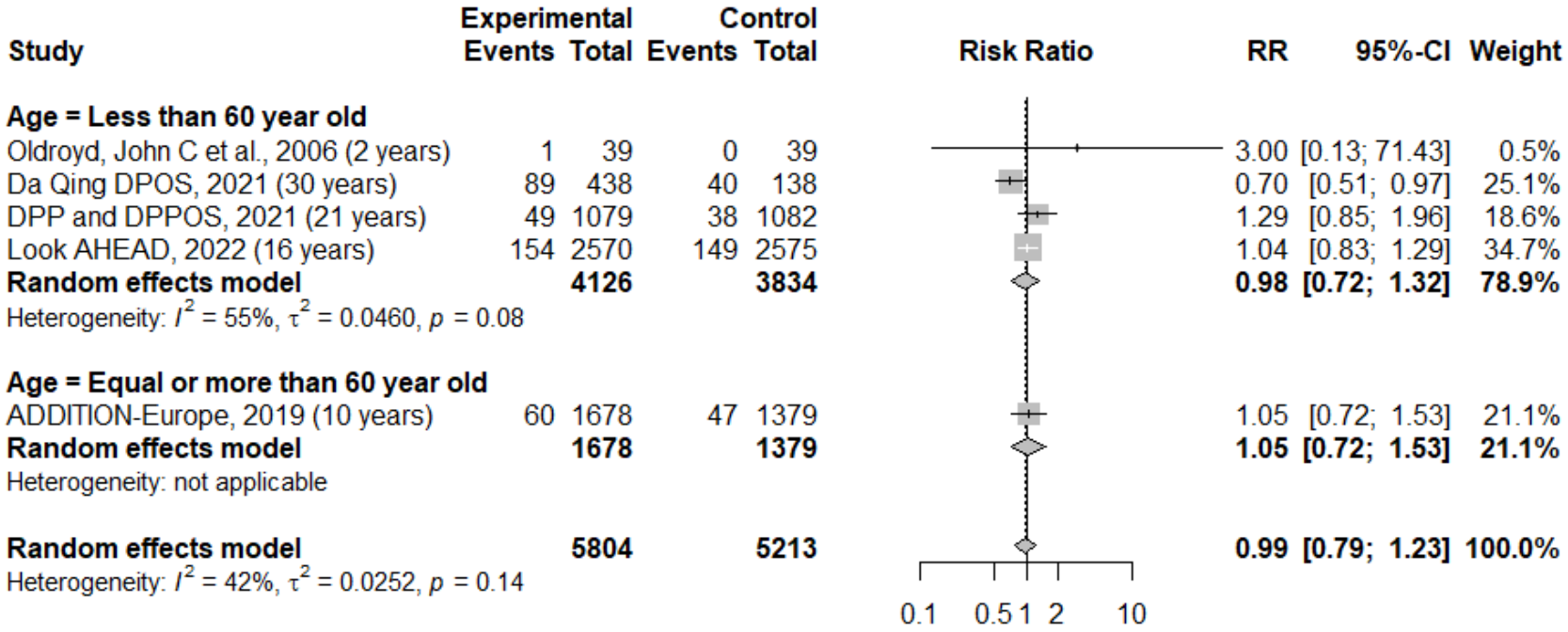
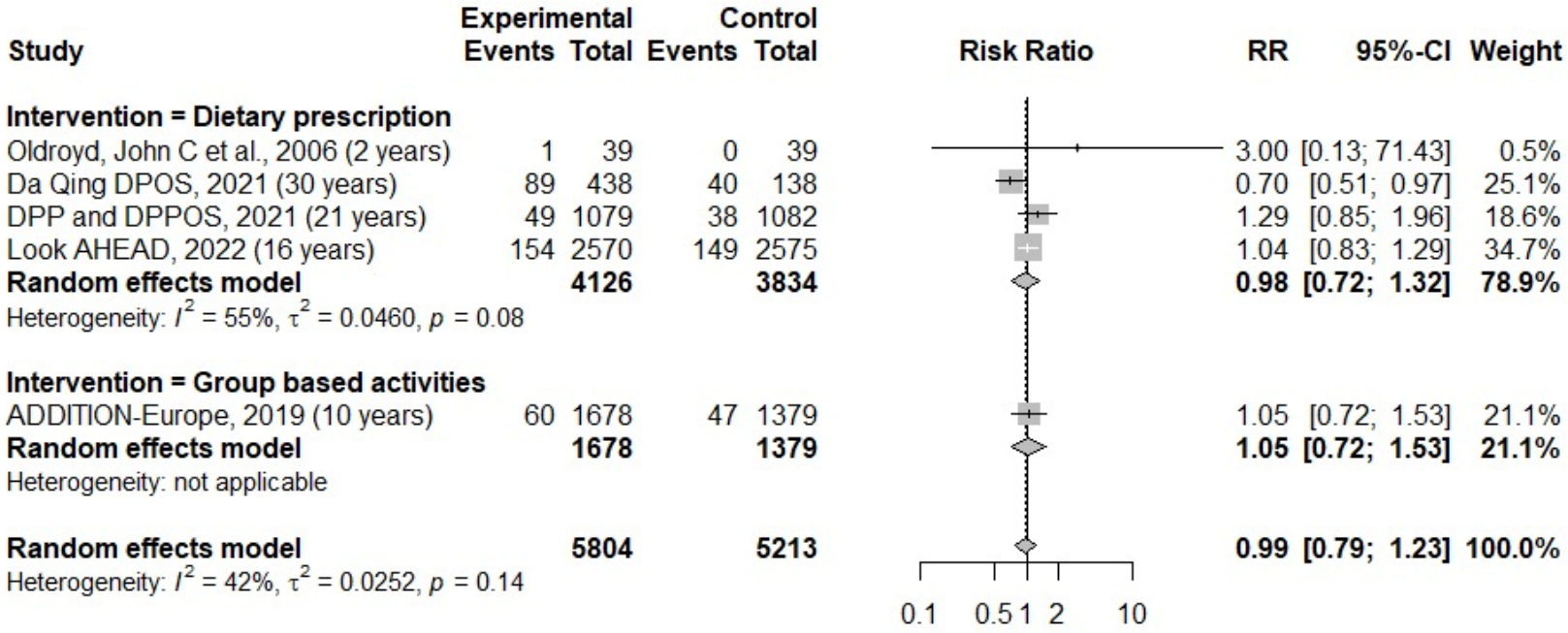


Figure S18. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model by the mean age of participants (adults or elderly, according to the cutoff of 60 years-old).



Studies were considered as “dietary prescription” if they had individualized counseling or caloric and nutrient targets as part of intervention groups.

Figure S19. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the dietary intervention modality of the studies.

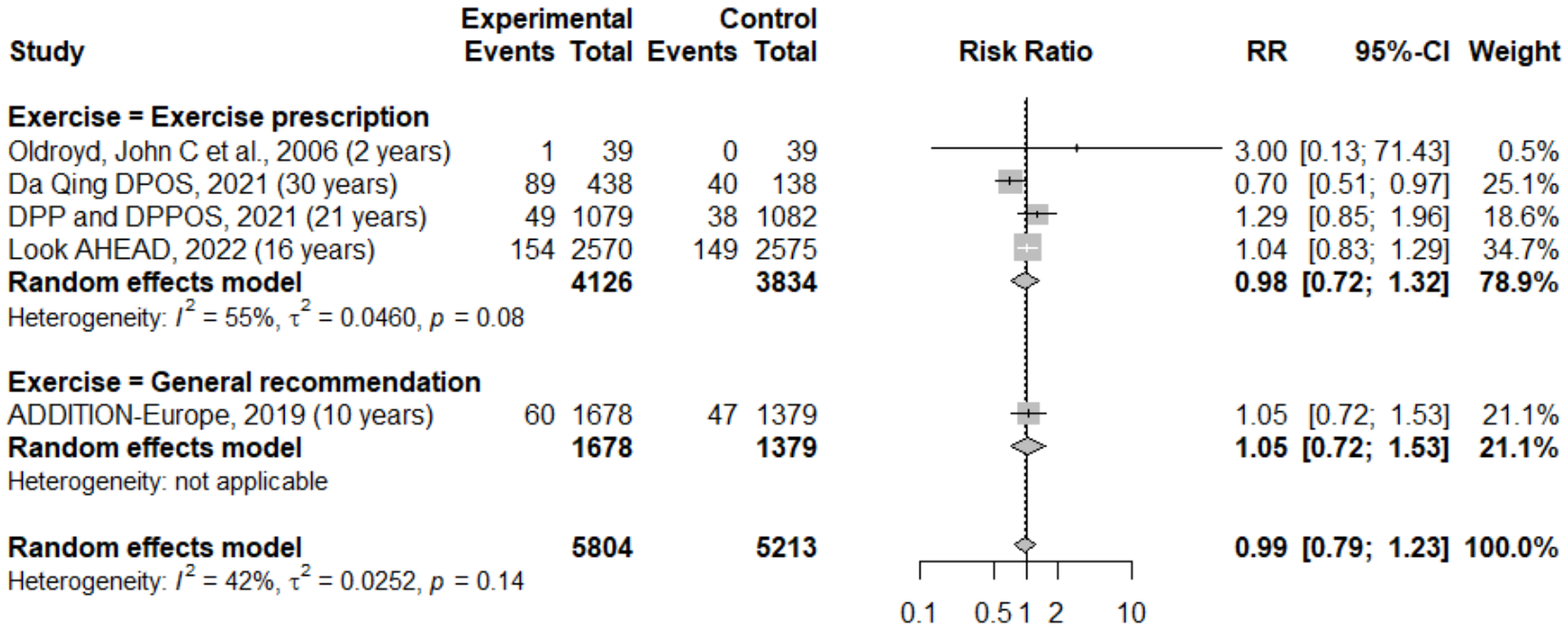


Figure S20. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the physical exercise intervention modality of the studies.

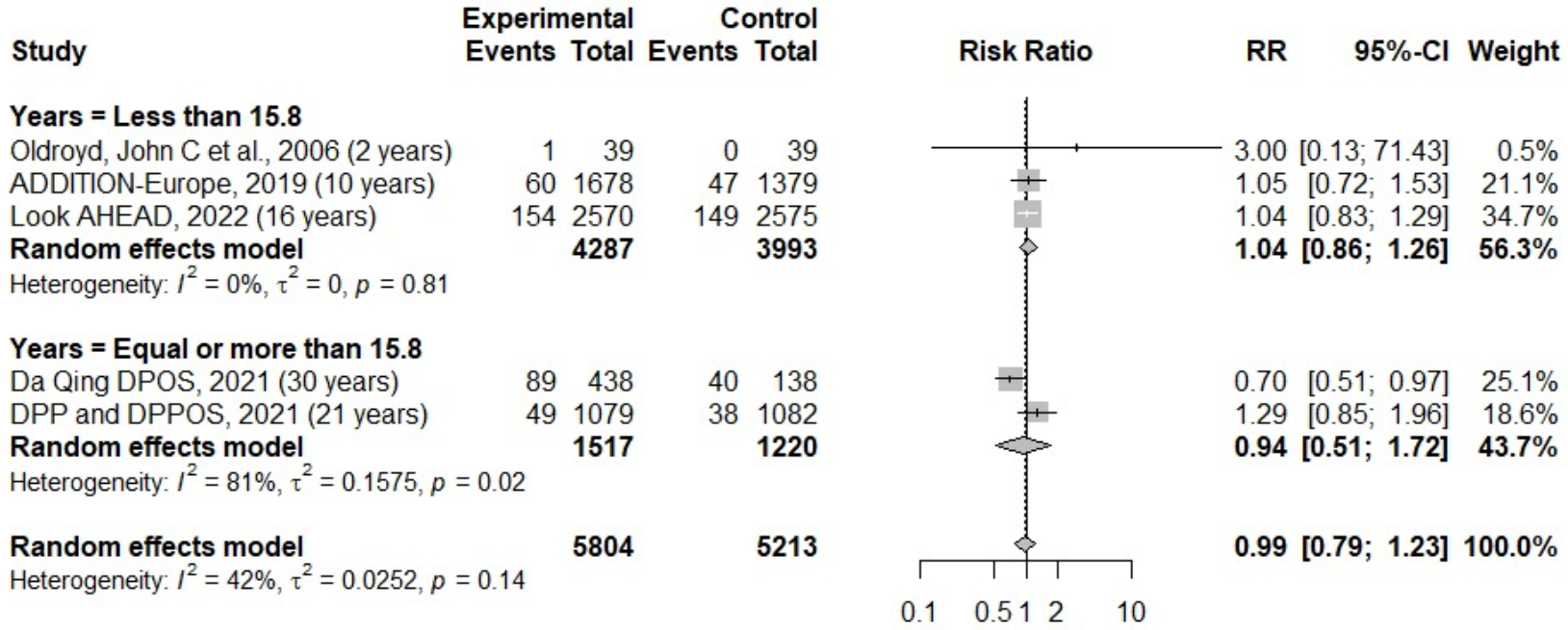


Figure S21. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the mean follow-up of the studies.

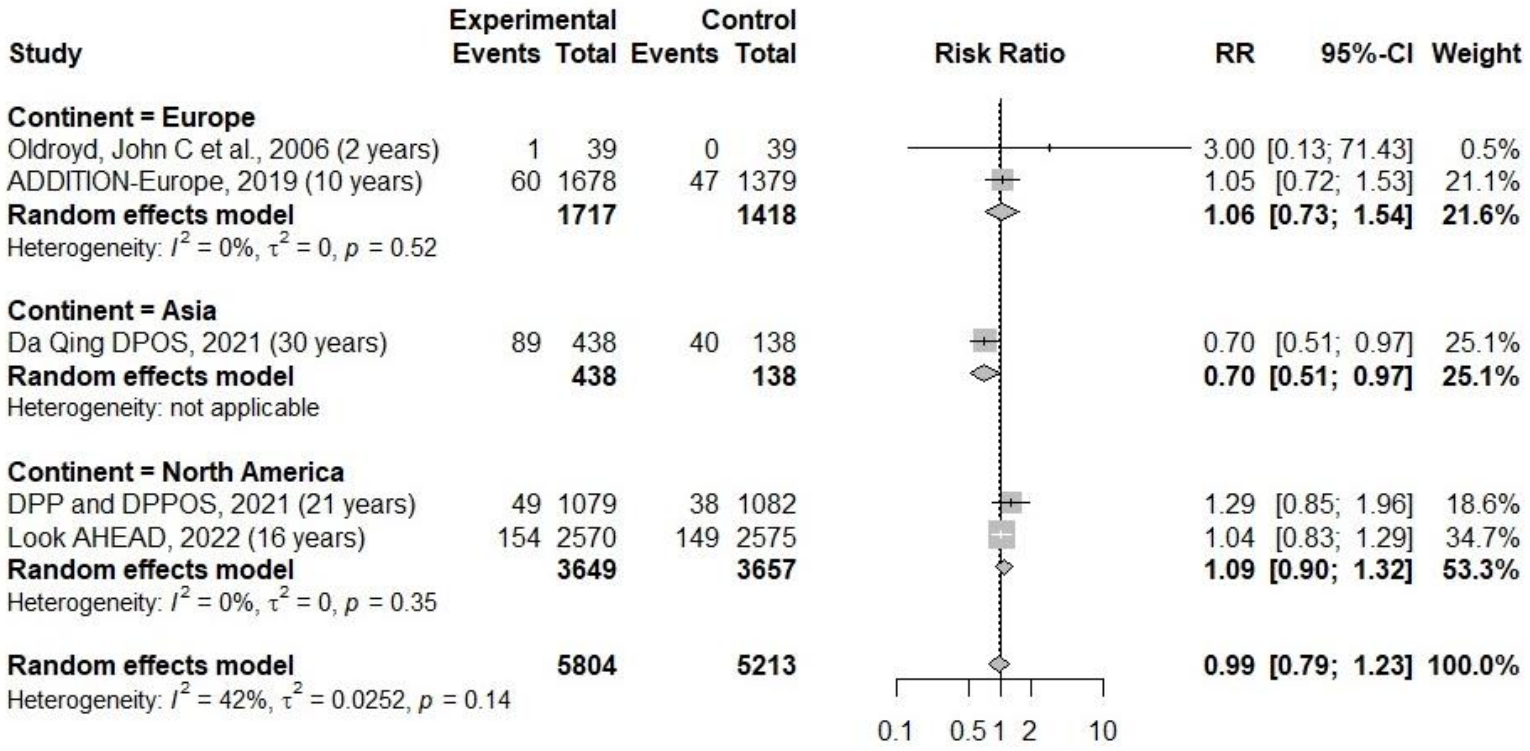


Figure S22. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality using a random-effect model according to the geographic location of the studies.

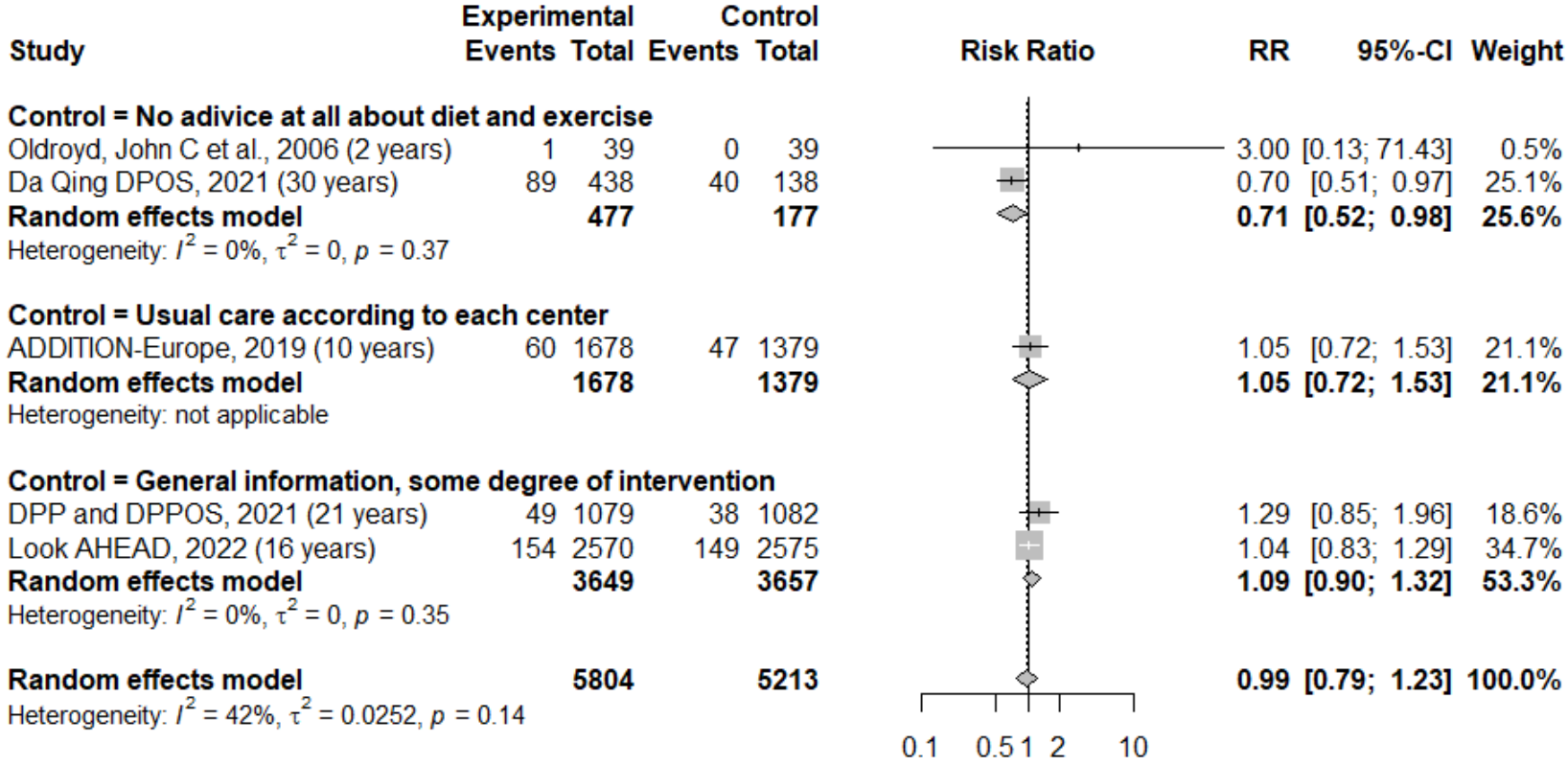
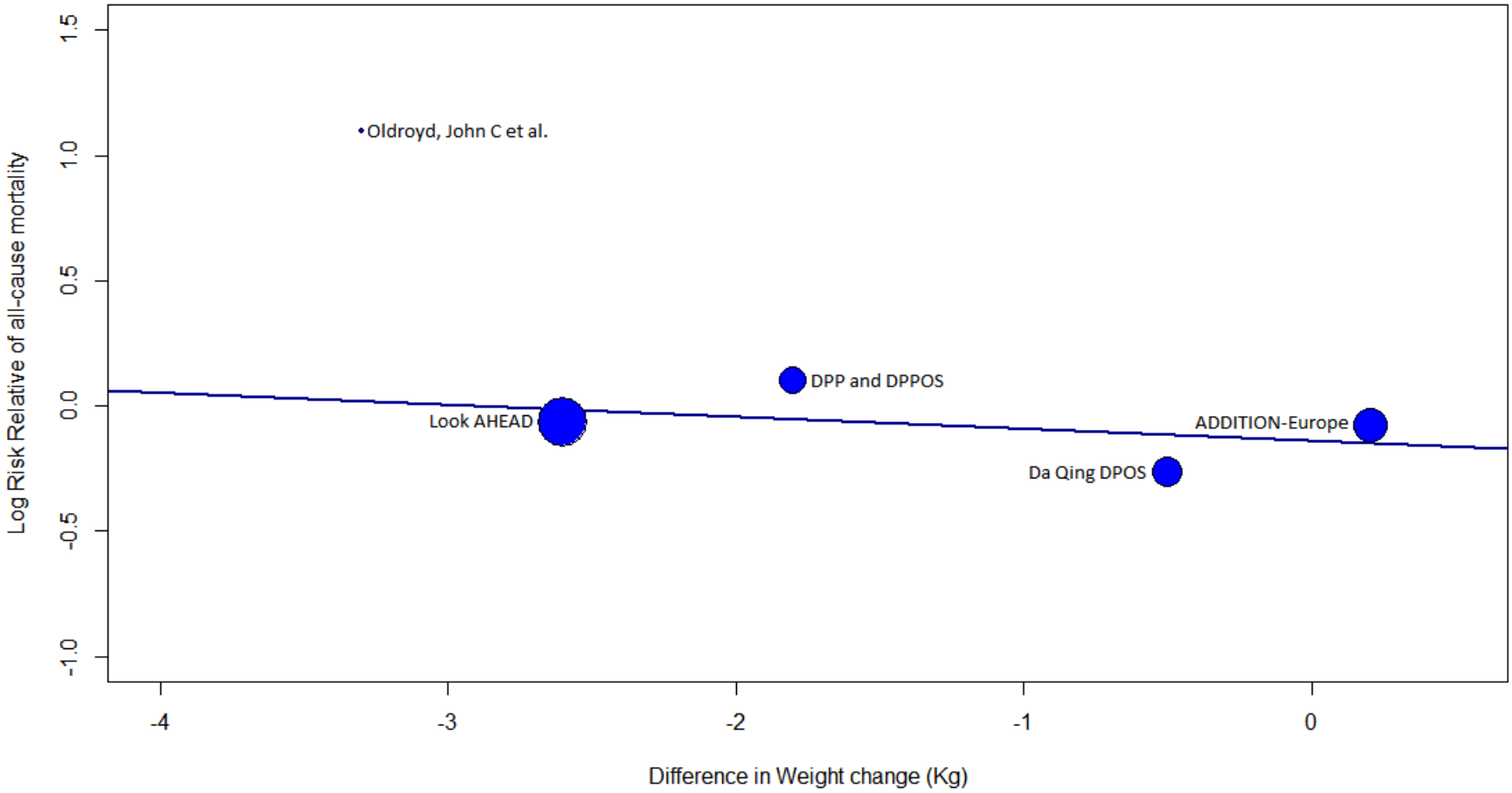


Figure S23. Subgroup analysis of the effect of intensive lifestyle interventions on cardiovascular mortality according to the control group of the studies.



Look AHEAD, Look Action for Health in Diabetes; ADDITION-EUROPE, Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care; Da Qing DPOS, China Da Qing Diabetes Prevention Outcomes Study; DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study.

Figure S24. Meta regression of the relationship between mean weight change (intervention - control) and relative risk of cardiovascular mortality.