Bone & Joint Research

Supplementary Material

10.1302/2046-3758.129.BJR-2023-0118.R1

Table i. Search strategy used in each database searched.

Database	Search strategy	Articles retrieved
PubMed	(("Mendelian Randomization Analysis"[Mesh]) OR (((((Analysis, Mendelian Randomization[Title/Abstract]) OR (Mendelian Randomization[Title/Abstract])) OR (Genetic Instrumental*[Title/Abstract])) OR (Genetic Instrumental Variable*[Title/Abstract])) OR (genetic instrument*[Title/Abstract]))) AND (("Arthritis, Rheumatoid"[Mesh]) OR (Rheumatoid Arthritis[Title/Abstract]))	102
Web of Science	#1. (((((TS=(Mendelian Randomization Analysis)) OR TS=(Analysis, Mendelian Randomization)) OR TS=(Mendelian Randomization)) OR TS=(Genetic Instrumental)) OR TS=(Genetic Instrumental Variable)) OR TS=(genetic instrument) #2. (TS=(Arthritis, Rheumatoid)) OR TS=(Rheumatoid Arthritis) #3. #2 AND #1	250
Embase	#1. 'mendelian randomization analysis'/exp #2. 'rheumatoid arthritis'/exp #3. 'analysis, mendelian randomization':ab,ti OR 'mendelian randomization':ab,ti OR 'genetic instrumental':ab,ti OR 'genetic instrumental variable':ab,ti OR 'genetic instrument':ab,ti #4. 'rheumatoid arthritis':ab,ti #5. #1 OR #3 #6. #2 OR #4 #7. #5 AND #6	165

Table ii. Quality Assessment tool conducted based on adherence to the Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) Guidelines for all 19 studies included in the meta-analysis. Each item is scored between 0 and 1 for each criterion to yield a total score. Upon conversion of the quality assessment score to a percentage, scores of < 75%, 75 to 85%, and > 85% were considered to indicate high, medium, and low risk of bias, respectively.

Study and year of publication	1. Title & abstract	2. Background & objective	3. Design & data sources	4. Study sample	5. Selection of genetic variants	6. Primary analysis	7. Sensitivity analyses	8. Software and pre-registration	9. Data presentati on	10. Limitations, interpretatio n	Total score (out of 10)	% score*
Martin et al, 2022[1]	1	1	1	1	0.5	1	0.5	1	1	1	9	90
Tang et al, 2021[2]	1	1	1	1	1	1	1	1	1	0.5	9.5	95
Bae & Lee, 2019[3]	1	1	1	1	1	1	1	1	1	1	10	100
Zhao et al, 2022[4]	1	1	1	1	1	1	1	1	1	0.5	9.5	95
Qian et al, 2020[5]	1	1	1	1	1	1	0.5	1	0.5	1	9	90
Jiang et al, 2021[6]	1	0.5	1	1	1	1	1	1	0.5	0.5	8.5	85
Bae & Lee, 2019[7]	1	1	1	1	1	1	1	1	1	1	10	100
Pu et al, 2022[8]	1	1	1	1	1	1	0.5	1	1	1	9.5	95
Bae & Lee, 2018[9]	1	0.5	1	1	1	1	1	0	1	1	8.5	85
Huang et al, 2021[10]	1	1	1	1	1	1	1	1	1	1	10	100
Bae & Lee, 2019[11]	1	1	1	1	1	1	1	0.5	1	1	9.5	95
Yuan et al, 2021[12]	0.5	0.5	1	1	1	1	0.5	1	1	1	8.5	85
Zhou et al, 2021[13]	1	1	1	1	1	1	0.5	1	1	1	9.5	95
Cheng et al, 2019[14]	1	1	1	1	1	1	0.5	1	1	1	9.5	95
Yuan & Larsson, 2020[15]	1	1	1	1	1	1	0.5	0.5	1	1	9	90
Ye et al, 2021[16]	1	1	1	1	1	1	0.5	1	0.5	1	9	90
Bae & Lee, 2020[17]	1	0.5	1	1	1	1	1	0	1	1	8.5	85
Yin et al, 2022[18]	1	1	1	1	1	1	1	1	1	1	10	100
Wu et al, 2021[19]	1	1	1	1	1	0.5	0.5	1	1	1	9	90

*Study quality was assessed using a modified version of the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.[20,21] A score was given if the following were satisfied:

1. The title and/or abstract indicate Mendelian randomization (MR) design.

2. The background and rationale for the study and the objective are clearly reported.

3. The study design and data source(s) used are clearly reported.

4. The study sample, including the number of cases and non-cases or total number of participants included in the analysis, is reported.

5. The selection of genetic variants as well as the number of genetic variants used in the MR analysis are reported.

6. The statistical methods used for the primary analysis and the exposure unit are reported.

7. Sensitivity analyses based on robust MR methods (e.g. the weighted median and/or MR-Egger regression) were conducted and reported.

8. The software used for the MR analysis is reported.

9. Relative risk (odds ratio) estimates are clearly presented in tables or figures.

10. The limitations of the study are discussed and the overall interpretation of results considering the objective and limitations is sound.

Table iii. Mendelian randomization studies included in the meta-analyses of genetically predicted obesity-related indicators, life environment, serum minerals, and disease status in relation to rheumatoid arthritis.

Phenotype	Consortium (X)	Cases, n	SNPs, n	OR	LB	UB	p-value	p-value for MR-Egger intercept*	p-value for heterogeneity analysis	Unit	Study, yr
Obesity-related											
BMI	IEU	339,224	N/A	1.20	0.95	1.52	0.137	0.112	0.005	4.2 kg/m^2	Martin et al, 2022[1]
BMI	IEU	339,224	N/A	1.27	0.99	1.63	0.062	0.736	0.357	4.2 kg/m^2	Martin et al, 2022[1]
BMI	IEU	339,224	N/A	1.40	1.15	1.70	0.001	N/A	N/A	4.2 kg/m^2	Martin et al, 2022[1]
BMI	UK Biobank	806,810	696	1.27	1.12	1.45	2.400×10^{-4}	0.550	<0.001	4.2 kg/m^2	Tang et al, 2021[2]
BMI	IEU	322,154	68	1.03	1.03	1.03	0.033	0.736	0.512	4.2 kg/m^2	Bae & Lee, 2019[3]
BMI	IEU	766,345	463	1.14	0.95	1.36	0.160	0.741	3.21×10^{-44}	4.2 kg/m^2	Zhao et al, 2022[4]
BMI	**Meta-analysis**	**2,234,533**		**1.25**	**1.16**	**1.36**	**$< 1.00 \times 10^{-5}$**				
Body fat percentage	UK Biobank	442,278	N/A	1.40	1.15	1.71	0.001	6.00×10^{-48}	0.933	SD	Martin et al, 2022[1]
Body fat percentage	UK Biobank	442,278	N/A	1.56	1.30	1.87	1.00×10^{-6}	0.0002	0.326	SD	Martin et al, 2022[1]
Body fat percentage	UK Biobank	442,278	N/A	1.77	1.56	2.00	4.00×10^{-18}	N/A	N/A	SD	Martin et al, 2022[1]
Body fat percentage	**Meta-analysis**	**442,278**		**1.63**	**1.49**	**1.79**	**$< 1.00 \times 10^{-5}$**				
Favourable adiposity	Martin et al, GWAS[22]	442,278	N/A	2.06	1.08	3.92	0.034	0.011	0.029	SD	Martin et al, 2022[1]
Favourable adiposity	Martin et al, GWAS[22]	442,278	N/A	1.85	0.97	3.53	0.069	0.389	0.168	SD	Martin et al, 2022[1]
Favourable adiposity	Martin et al, GWAS[22]	442,278	N/A	1.61	1.01	2.56	0.055	N/A	N/A	SD	Martin et al, 2022[1]
Favourable adiposity	**Meta-analysis**	**442,278**		**1.78**	**1.28**	**2.46**	**6.00×10^{-4}**				
Unfavourable adiposity	Martin et al, GWAS[22]	442,278	N/A	1.43	0.89	2.32	0.152	0.767	1.00×10^{-4}	SD	Martin et al, 2022[1]
Unfavourable adiposity	Martin et al, GWAS[22]	442,278	N/A	1.82	1.11	2.96	0.023	0.658	0.062	SD	Martin et al, 2022[1]
Unfavourable adiposity	Martin et al, GWAS[22]	442,278	N/A	1.66	1.19	2.31	0.005	N/A	N/A	SD	Martin et al, 2022[1]

Unfavourable adiposity	**Meta-analysis**	**442,278**		**1.63**	**1.29**	**2.07**	**$< 1.00 \times 10^{-4}$**				
Life environment											
Lifetime smoking	UK Biobank	462,690	121	1.55	1.13	2.14	0.007	0.645	N/A	SD	Qian et al, 2020[5]
Lifetime smoking	UK Biobank	462,690	105	2.13	1.25	3.62	0.005	0.394	2.68×10^{-7}	SD	Zhao et al, 2022[4]
Lifetime smoking	**Meta-analysis**	**462,690**		**1.68**	**1.28**	**2.21**	**2.00×10^{-4}**				
Alcoholic drinks per week	IEU	941,280	80	0.85	0.56	1.29	0.450	0.080	N/A	1 cup/wk	Jiang et al, 2021[6]
Alcoholic drinks per week	IEU	335,394	25	1.03	0.59	1.80	0.908	N/A	N/A	1 cup/wk	Zhao et al, 2022[4]
Alcoholic drinks per week	**Meta-analysis**	**1,276,674**		**0.91**	**0.65**	**1.27**	**0.590**				
Coffee intake	UK Biobank	428,860	27	1.47	0.79	2.75	0.218	0.245	0.049	1 cup/day	Pu et al, 2022[8]
Coffee intake	Coffee and Caffeine Genetics Consortium; Amin et al, GWAS[23]	109,638	3	2.16	1.25	3.73	0.006	0.451	0.573	1 cup/day	Bae & Lee, 2018[9]
Coffee intake	**Meta-analysis**	**538,498**		**1.82**	**1.21**	**2.74**	**0.004**				
Educational attainment	IEU	1,131,881	373	0.42	0.34	0.52	1.78×10^{-14}	0.030	0.340	4.2 yrs	Huang et al2021[10]
Educational attainment	IEU	1,131,881	659	0.50	0.41	0.60	1.150×10^{-13}	0.281	N/A	4.2 yrs	Yuan et al, 2021[12]
Educational attainment	IEU	766,345	1005	0.37	0.32	0.45	6.200×10^{-29}	0.149	1.87×10^{-73}	4.2 yrs	Zhao et al, 2022[4]
Educational attainment	**Meta-analysis**	**1,898,226**		**0.43**	**0.36**	**0.51**	**$< 1.00 \times 10^{-5}$**				
Serum minerals											
Serum Ca	O'Seaghdha et al, GWAS[24]	61,079	8	0.73	0.46	1.14	0.160	0.985	0.876	SD	Zhou et al, 2021[13]
Serum Ca	O'Seaghdha et al, GWAS[24]	39,400	6	1.83	0.99	3.41	0.055	0.590	0.638	SD	Cheng et al, 2019[14]
Serum Ca	**Meta-analysis**	**100,479**		**1.13**	**0.46**	**2.78**	**0.790**				
Serum iron	IEU	48,972	3	0.79	0.65	0.94	0.010	0.712	0.096	SD	Yuan et al, 2020[15]
Serum iron	IEU	48,972	3	0.98	0.77	1.25	0.850	0.517	0.220	SD	Zhou et al, 2021[13]
Serum iron	IEU	48,972	11	1.01	0.82	1.25	0.913	0.150	6.84×10^{-6}	SD	Cheng et al, 2019[14]
Serum iron	**Meta-analysis**	**48,972**		**0.91**	**0.80**	**1.03**	**0.130**				
Serum copper	IEU	2,603	2	1.01	0.84	1.23	0.870	N/A	0.628	SD	Zhou et al, 2021[13]
Serum copper	IEU	2,603	2	0.94	0.77	1.16	0.579	N/A	0.130	SD	Cheng et al, 2019[14]
Serum copper	**Meta-analysis**	**2,603**		**0.98**	**0.85**	**1.12**	**0.740**				
Serum magnesium	Meyer et al, GWAS[25]	23,829	6	0.96	0.56	1.65	0.870	0.140	0.158	SD	Zhou et al, 2021[13]

Serum magnesium	International CHARGE Alliance	15,366	4	3.07	0.16	58.62	0.457	N/A	0.044	SD	Cheng et al, 2019[14]
Serum magnesium	**Meta-analysis**	**39,195**		**1.00**	**0.59**	**1.69**	**0.990**				
Serum zinc	IEU	2603	2	0.96	0.75	1.01	0.750	NA	0.977	SD	Zhou et al.2021[13]
Serum zinc	IEU	2603	2	1.07	0.94	1.22	0.328	NA	0.460	SD	Cheng et al.2019[14]
Serum zinc	**Meta-analysis**	**2603**		**1.05**	**0.93**	**1.17**	**0.450**				
Serum selenium	CARDIA, JoCo, NHS, HPFS	9639	11	1.03	0.97	1.10	0.359	0.611	0.757	SD	Ye et al.2021[16]
Serum selenium	QIMR and ALSPAC	5477	2	0.98	0.86	1.11	0.733	NA	NA	SD	Ye et al.2021[16]
Serum selenium	**Meta-analysis**	**15116**		**1.02**	**0.97**	**1.08**	**0.450**				
Comorbidity											
Chronic periodontitis	SHIP GWAS SHIP-TREND cohorts*	4032	20	1.02	0.99	1.05	0.270	0.500	0.790	NA	Yin et al.2022[18]
Chronic periodontitis	Teumer et al. GWAS[26]	3915	7	1.18	1.01	1.38	0.035	0.078	□ 0.001	NA	Bae & Lee.2020[17]
Chronic periodontitis	**Meta-analysis**	**7947**		**1.08**	**0.94**	**1.24**	**0.300**				
Graves' Disease	BBJ	212453	12	1.30	0.94	1.80	0.112	0.663	0.120	NA	Wu et al.2021[19]
Graves' Disease	BBJ	212453	13	1.35	0.95	1.94	0.097	0.702	0.130	NA	Wu et al.2021[19]
Graves' Disease	**Meta-analysis**	**212453**		**1.32**	**1.04**	**1.68**	**0.020**				

*SHIP-TREND cohorts comprise the two independent cohorts SHIP (recruitment 1997 to 2001) and SHIP-TREND (recruitment 2008 to 2012) with re-evaluations in five-year intervals.

ALSPAC, Avon Longitudinal Study of Parents and Children; BBJ, BioBank Japan; Ca, calcium; CARDIA, Coronary Artery Risk Development in Young Adults; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; GWAS, genome-wide association studies; HPFS, Health Professionals Follow-up Study; IEU, IEU OpenGWAS project; JoCo, Johnston County Osteoarthritis Project; LB, low bound; MR, Mendelian randomization; NHS, Nurses' Health Study; N/A, not available; OR, odds ratio; QIMR, QIMR Berghofer Medical Research Institute; SHIP, Study of Health in Pomerania; SNP, single nucleotide polymorphism; UB, up bound.

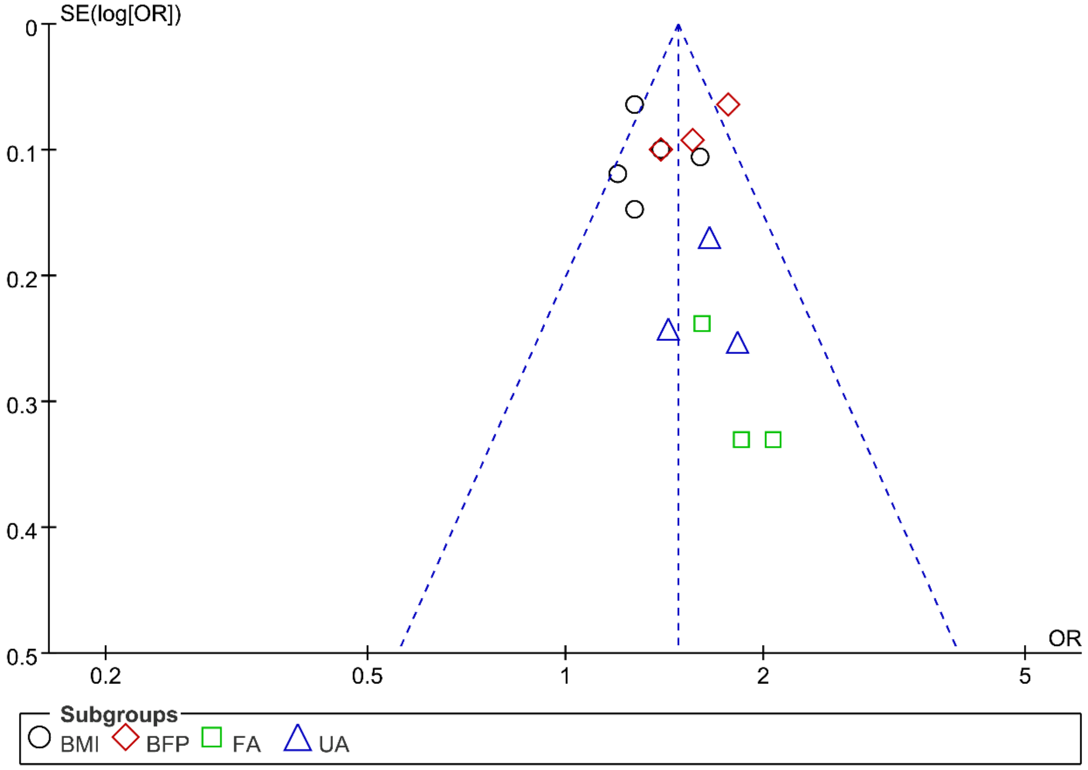


Fig a. Funnel plot of the included studies on obesity-related indicators. BFP, body fat percentage; FA, favourable adiposity; OR, odds ratio; SE, standard error; UFA, unfavourable adiposity.

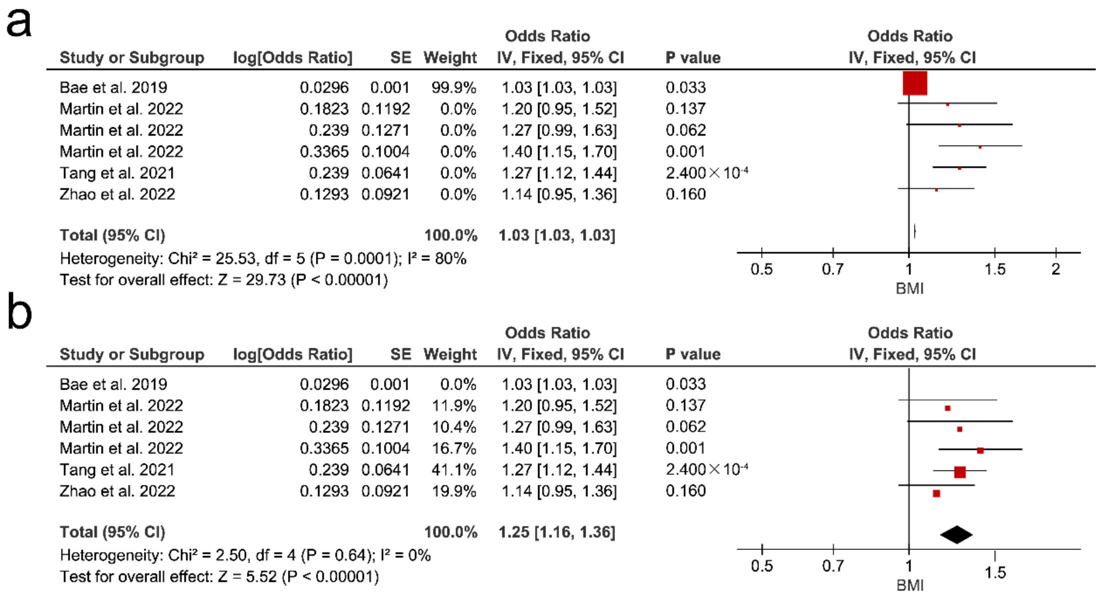


Fig b. Forest plot before and after the removal of heterogeneity of BMI. a) Forest plot of causal relationship between BMI genetic susceptibility and rheumatoid arthritis (RA) risk before removing heterogeneity. b) Forest plot of causal relationship between BMI genetic susceptibility and RA risk after removing heterogeneity. CI, confidence interval; IV, inverse variance; SE, standard error.

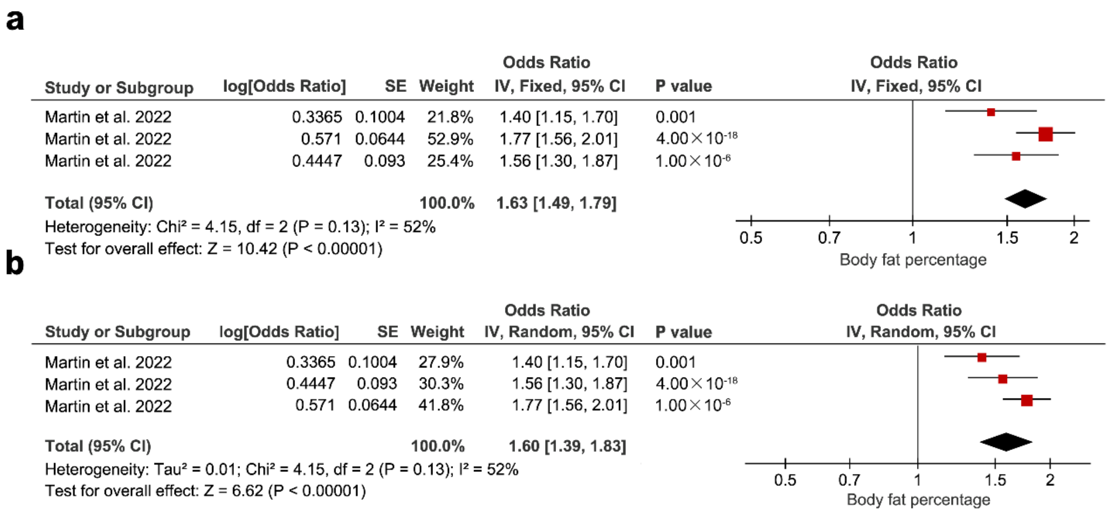
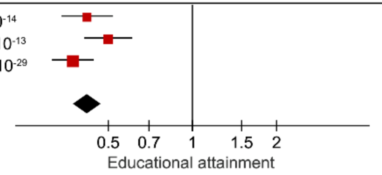


Fig c. Forest plots of body fat percentage (BFP) in different models. a) Forest plot of causal relationship between BFP genetic susceptibility and rheumatoid arthritis (RA) risk (fixed-effect model). b) Forest plot of causal relationship between BFP genetic susceptibility and RA risk (random-effect model). CI, confidence interval; IV, inverse variance; SE, standard error.

a

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	P value
Huang et al. 2021	-0.8675	0.1078	27.4%	0.42 [0.34, 0.52]	1.78×10^{-14}
Yuan et al. 2021	-0.6931	0.1013	31.1%	0.50 [0.41, 0.61]	1.150×10^{-13}
Zhao et al. 2022	-0.9835	0.0876	41.5%	0.37 [0.31, 0.44]	6.200×10^{-29}
Total (95% CI)			**100.0%**	**0.42 [0.38, 0.47]**	

Heterogeneity: Chi² = 4.71, df = 2 (P = 0.10); I² = 58%
Test for overall effect: Z = 15.26 (P < 0.00001)



b

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	P value
Huang et al. 2021	-0.8675	0.1078	30.8%	0.42 [0.34, 0.52]	1.78×10^{-14}
Yuan et al. 2021	-0.6931	0.1013	32.6%	0.50 [0.41, 0.61]	1.150×10^{-13}
Zhao et al. 2022	-0.9835	0.0876	36.6%	0.37 [0.31, 0.44]	6.200×10^{-29}
Total (95% CI)			**100.0%**	**0.43 [0.36, 0.51]**	

Heterogeneity: Tau² = 0.01; Chi² = 4.71, df = 2 (P = 0.10); I² = 58%
Test for overall effect: Z = 9.77 (P < 0.00001)

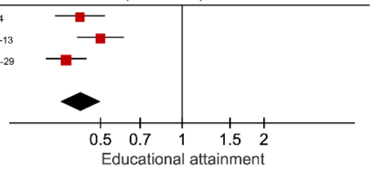


Fig d. Forest plots of educational attainment in different models. a) Forest plot of causal relationship between educational attainment genetic susceptibility and rheumatoid arthritis (RA) risk (fixed-effect model). b) Forest plot of causal relationship between educational attainment genetic susceptibility and RA risk (random-effect model). CI, confidence interval; IV, inverse variance; SE, standard error.

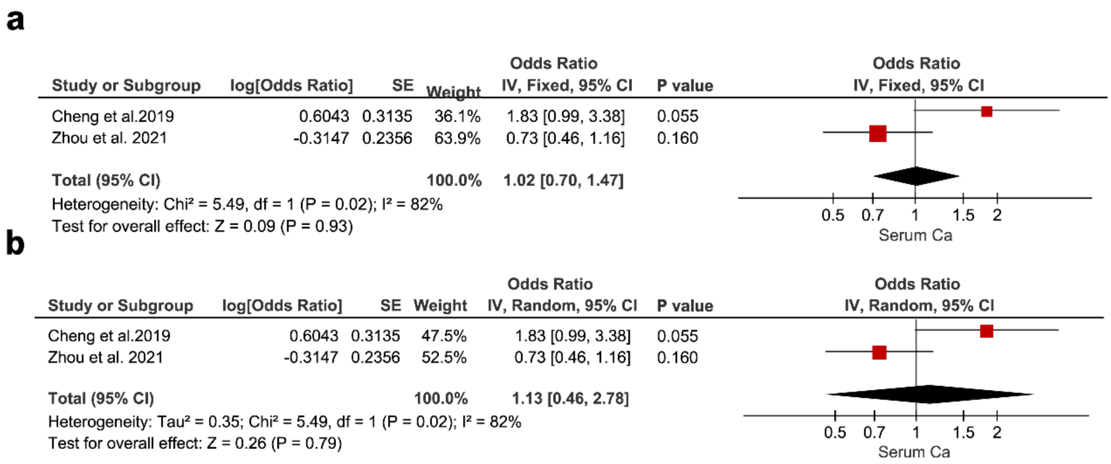


Fig e. Forest plots of serum calcium (Ca) in different models. a) Forest plot of causal relationship between serum Ca genetic susceptibility and rheumatoid arthritis (RA) risk (fixed-effect model). b) Forest plot of causal relationship between serum Ca genetic susceptibility and RA risk (random-effect model). CI, confidence interval; IV, inverse variance; SE, standard error.

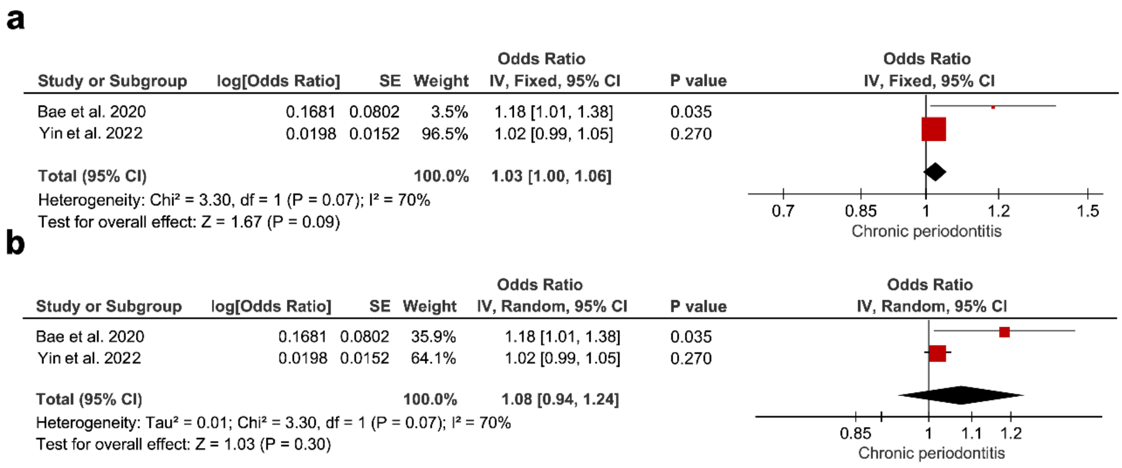


Fig f. Forest plots of chronic periodontitis in different models. a) Forest plot of causal relationship between chronic periodontitis genetic susceptibility and rheumatoid arthritis (RA) risk (fixed-effect model). b) Forest plot of causal relationship between chronic periodontitis genetic susceptibility and RA risk (random-effect model). CI, confidence interval; IV, inverse variance; SE, standard error.

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