SUPPLEMENTAL FILE

Title: MicroRNA Expression Signatures in Atrial Fibrillation: A Critical Systematic Review and Bioinformatics Analysis

Contents

Tables

Figures

Abbreviations in Supplementary Figures

AF: atrial fibrillation; miRNA: microRNAs; 3'-UTRs: 3'-untranslated regions; LAA: left atrial appendage; RA: right atrial; LA: left atrial;

qRT-PCR: real-time polymerase chain reaction; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; DM: diabetes mellitus; LVEF: left ventricular ejection fraction.

Supplementary Table 1. Search strategy used onApril 30th, 2019

Literature databases	**Search items**	**Items found**
MEDLINE	(“microRNA”[MeSH Terms] OR “microRNA”[Title/Abstract] OR “miRNA”[Title/Abstract] OR “miR-”[Title/Abstract]) AND (“atrial fibrillation”[Title/Abstract] OR “atrial fibrillation”[MeSH Terms] OR “AF”[Title/Abstract]) AND (“expression”[Title/Abstract] OR “profile” [Title/Abstract] OR “profiling”[Title/Abstract])	150
EMBASE	(‘microRNA’/exp OR ‘microRNA’:ti, ab,kw OR ‘miRNA’: ti,ab,kw OR ‘miR-’: ti,ab,kw) AND (‘atrial fibrillation’/exp OR ‘atrial fibrillation’:ti, ab,kw OR ‘AF’: ti,ab,kw) AND (‘expression’ : ti,ab,kw OR ‘profile’ : ti,ab,kw OR ‘profiling’: ti,ab,kw)	164
COCHRANE	(MeSH descriptor: [microRNA] OR microRNA: ti,ab,kw OR miRNA: ti,ab,kw OR miR-: ti,ab,kw) AND (MeSH descriptor: [atrial fibrillation] OR atrial fibrillation: ti,ab,kw OR AF: ti,ab,kw) AND (expression : ti,ab,kw OR profile: ti,ab,kw OR profiling: ti,ab,kw)	10
Overall		324

Supplementary Table 2. Excluded studies with reasons

Study	Sample type	Reason for exclusion
Zhu Y 2018[1]	atrial tissue	Not reported sample size
Zhu H 2018[2]	atrial tissue	Not reported cut-off criteria
Xu G 2013[3]	atrial tissue	Not reportednon-AF control samplesfor comparison
Wang W 2018[4]	atrial tissue	Not reportednon-AF control samplesfor comparison
Wang T 2016[5]	atrial tissue	Not reported sample size
Wang M 2018[6]	atrial tissue	Not reportednon-AF control samplesfor comparison
Wang J 2012[7]	left atrial appendage	Repeated studies
Wang J 2015[8]	atrial tissue	Repeated studies
Wang J 2014[9]	atrial tissue	Not reported expression level profiling
Velagaleti R 2014[10]	plasma	Not reported expression level profiling
Tsoporis J 2018[11]	plasma	Not reportednon-AF control samplesfor comparison
Tsoporis J 2013[12]	atrial tissue	Not reportednon-AF control samplesfor comparison
Torrado M 2015[13]	left atrial samples	Not reportednon-AF control samplesfor comparison
Rizos I 2013[14]	right atrial	Not reportednon-AF control samplesfor comparison
Reilly S 2015[15]	atrial tissue	Not reported sample size
Pidikiti R 2013[16]	plasma	Not reported expression level profiling
Liu H 2014[17]	left atrial samples	Not reportednon-AF control samplesfor comparison
Lei L 2016[18]	Peripheral blood	Not reportednon-AF control samplesfor comparison
Chiang D 2014[19]	atrial tissue	Repeated studies
Berger W 2015[20]	atrial tissue	Not reportednon-AF control samplesfor comparison

Supplementary Table 3. Patient demographics and clinical characteristics of included studies.

Study	Total number	Mean age(y)	Female (%)	Smoking (%)	Renal disease (%)	BMI (kg/m2) (mean)	SBP (mmHg) (mean)	DBP (mmHg) (mean)	Hypertension (%)	DM (%)	Dyslipidemia (%)	History of Stroke (%)	mitral stenosis %	LVEF (%)
Zhao Y et al.2015	6	46.7	100	NR	25.0	0.3	118.2	71.4	NR	NR	36.9	NR	33.4	NR
Yamac et al.2016	63	59.9	21.8	75.9	7.2	29.2	NR	NR	49.4	57.9	NR	4.7	NR	56.8
Xu G et al.2016	180	70.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Xie H et al.2018	50	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Xiao J et al.2011	18	49.3	66.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	50.0	NR
Wei X et al.2015	33.5	62.7	50.0	25.4	NR	222	124.6	78.3	43.5	22.4	NR	22.2	NR	59.4
Wei J et al.2018	30	66.1	45.8	34.7	NR	NR	NR	NR	59.7	30.6	NR	43.1	NR	55.5
Wang X et al.2013	73	58.6	47.5	25.5	NR	NR	128.2	70.5	23.3	6.1	NR	25.5	NR	57.4
Wang J et al.2015	47	45.2	30.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	66.2
Wang F et al.2017	43	52.4	50.9	26.4	NR	NR	NR	NR	21.0	8.7	1.8	26.4	NR	NR
Tao H et al.2018	49	50.1	51.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	54.6
Stillitano F etal.2013	80	68.0	38.5	NR	NR	NR	NR	NR	53.4	20.0	NR	NR	NR	51.8
Soeki et al.2016	70	63.5	28.7	NR	NR	NR	NR	NR	57.5	20.0	NR	5.0	NR	NR
Slagsvold K et al.2014	37	70.5	24.5	NR	NR	NR	NR	NR	49.0	14.5	NR	NR	NR	50.5
Reilly S et al.2016	227	71	32.5	48.5	NR	NR	NR	NR	67.5	16.0	61.0	NR	NR	NR
Qiao G et al.2017	10	59.5	50.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	57.4
Nishi H et al.2013	19	66.5	39.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	65.8
Natsume Y et al.2018	50	55.5	36.0	2	NR	NR	NR	NR	31.0	14.0	29.0	2.0	NR	NR
McManus D et al.2015	211	58.5	42.0	17.0	NR	NR	131.5	75.5	70.0	27.0	NR	NR	NR	NR
McManus D et al.2014	2338	69.2	59.0	6.4	NR	28.9	128.5	71.5	46.4	19.0	NR	NR	NR	NR
Luo X et al.2013	22	47.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lu Y et al.2015	224	NR	45.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Liu Z et al.2012	60	39.8	36.7	NR	NR	NR	NR	NR	38.3	NR	NR	NR	NR	63.25
Liu T et al.2016	200	53.1	28.0	27.5	NR	NR	NR	NR	49.5	7.0	6.5	NR	NR	37.5
Liu H et al.2014	18	50.8	43.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	60.0
Ling T et al.2013	8	69.1	37.5	25.0	NR	NR	NR	NR	62.5	12.5	50.0	NR	12.5	NR
Li Y et al.2015	40	68.8	27.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	41.3
Li S et al.2017	37	50.0	54.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.1	63.1
Li N et al.2014	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Harling L et al.2017	22	61.5	22.5	22.5	NR	15.0	NR	NR	73.0	55.0	91.0	NR	NR	NR
Goren Y et al.2014	41	62.4	13.0	19.0	31.0	28.2	NR	NR	NR	39.5	80	NR	NR	NR
Girmatsion et al.2009	62	68.5	40.0	NR	NR	NR	NR	NR	55.1	17.8	32.3	NR	NR	60.0
Feldman A et al.2017	48	60.5	30.5	35.4	NR	NR	NR	NR	95.8	43.7	52.1	NR	NR	57.3
Dawson K et al.2013	47	66.1	31.8	NR	NR	NR	NR	NR	65.7	15.5	27.7	NR	NR	29.8
da Silva et al.2018	20	57.5	46.7	NR	NR	27.8	119.5	73.0	NR	NR	NR	NR	NR	66.0
Cooley N et al.2012	10	64.0	18.8	NR	NR	NR	NR	NR	50.0	12.5	45.9	NR	NR	NR
Chiang D et al.2015	18	66.0	37.5	NR	NR	28.9	NR	NR	90.7	33.8	55.5	NR	NR	49.8
Adam O et al.2012	10	65.3	20.0	NR	NR	28.8	NR	NR	NR	NR	NR	NR	NR	60.1

Supplementary Table 4. Quality assessment of miRNA studies according toQUADAS 2.

Studies	Was a consecutive or random sample of patients enrolled?	Did the studyavoidinappropriate exclusions?	Is the reference standard likely to correctly classify the targetcondition?	Were the referencestandard resultsinterpreted without knowledge of theresults of the indextest?	Was there an appropriate interval between index tests and reference standard?	Was the blind method used in result of referance standard?	Did allpatients receive thesame reference standard?	Were all patients included in the analysis?
Adam O *et al.*	Y	U	Y	Y	Y	Y	Y	Y
Cooley N *et al.*	Y	U	Y	Y	Y	Y	Y	Y
Chiang D *et al.*	N	U	Y	Y	Y	Y	Y	Y
da Silva A *et al.*	Y	N	Y	Y	Y	Y	Y	Y
Dawson K *et al.*	N	N	Y	Y	Y	Y	Y	Y
Feldman A *et al.*	Y	Y	Y	Y	Y	Y	Y	Y
Goren Y *et al.*	N	N	Y	Y	Y	Y	Y	Y
Girmatsion *et al.*	N	U	Y	Y	Y	Y	Y	Y
Harling L *et al.*	U	U	Y	Y	Y	Y	Y	Y
Li Y *et al.*	U	N	Y	Y	Y	Y	Y	Y
Li H *et al.*	Y	N	Y	Y	Y	Y	Y	Y
Li N *et al.*	N	N	Y	Y	Y	Y	Y	Y
Li S *et al.*	U	Y	Y	Y	Y	Y	Y	Y

Liu H *et al.*	U	N	Y	Y	Y	Y	Y	Y
Liu T *et al.*	U	U	Y	Y	Y	Y	Y	Y
Liu Z *et al.*	N	U	Y	Y	Y	Y	Y	Y
Lu Y *et al.*	N	N	Y	Y	Y	Y	Y	Y
Lu Y *et al.*	U	Y	Y	Y	Y	Y	Y	Y
LuoX *et al.*	U	U	Y	Y	Y	Y	Y	Y
McManus D *et al.*	N	U	Y	Y	Y	Y	Y	Y
McManus D *et al.*	N	N	Y	Y	Y	Y	Y	Y
Ling T *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Natsume Y *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Nishi H *et al.*	U	N	Y	Y	Y	Y	Y	Y
Qiao G *et al.*	U	N	Y	Y	Y	Y	Y	Y
Reilly S *et al.*	N	U	Y	Y	Y	Y	Y	Y
Slagsvold K *et al.*	Y	U	Y	Y	Y	Y	Y	Y
Soeki T *et al.*	Y	U	Y	Y	Y	Y	Y	Y
Stillitano F *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Tao H *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Wang J *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Wang F *et al.*	Y	U	Y	Y	Y	Y	Y	Y

Wang X *et al.*	U	N	Y	Y	Y	Y	Y	Y
Wei J *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Wei X *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Xiao J *et al.*	N	Y	Y	Y	Y	Y	Y	Y
Xie H *et al.*	Y	N	Y	Y	Y	Y	Y	Y
Xu G *et al.*	Y	U	Y	Y	Y	Y	Y	Y
Yamac A *et al.*	N	U	Y	Y	Y	Y	Y	Y
Zhao Y *et al.*	U	N	Y	Y	Y	Y	Y	Y

Y: Yes; N: No; U: Unclear.

Supplementary Table 5. Statistically significant up-regulated miRNAs in overall analysis (n=22)

miRNA	No. of studies	No. of samples	logOR	95%CI	*P* values
miR-664	3	278	7.131	(4.642, 9.620)	< 0.001
miR-638	2	40	6.081	(3.243, 8.918)	< 0.001
miR-572	2	40	6.081	(3.243, 8.918)	< 0.001
miR-486-5p	3	122	7.298	(5.002, 9.593)	< 0.001
miR-483-5p	3	50	5.654	(3.320, 7.987)	< 0.001
miR-454-5p	2	232	7.646	(1.338, 13.955)	0.018
miR-301b-3p	2	94	7.666	(4.863, 10.467)	< 0.001
miR-223-3p	6	227	6.473	(5.0560, 7.8900)	< 0.001
miR-208b-3p	2	27	5.146	(2.261, 8.031)	< 0.001
miR-193b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
miR-192-5p	2	106	6.611	(1.380, 11.841)	0.013
miR-18b-3p	2	46	6.220	(3.833, 9.056)	< 0.001
miR-155-3p	3	112	7.085	(4.786, 9.385)	< 0.001
miR-146b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
miR-146	2	234	7.827	(1.878, 13.775)	< 0.001
miR-144-5p	2	60	6.740	(3.918, 9.563)	< 0.001
miR-1308	2	28	5.336	(2.465, 8.207)	< 0.001
miR-1202	3	50	2.869	(1.309, 4.429)	< 0.001
miR-106b-3p	2	60	6.740	(3.918, 9.563)	< 0.001

miR-6767-5p	2	16	4.394	(1.473, 7.316)	0.003
miR-142-3p	2	94	7.666	(4.863, 10.469)	< 0.001
miR-451	2	60	6.740	(3.9183, 9.563)	< 0.001

Supplementary Table 6. Statistically significant down-regulated miRNAs in overall analysis (n=29)

miRNA	No. of studies	No. of samples	logOR	95%CI	*P* values
miR-484	2	28	5.336	(2.465, 8.207)	< 0.001
miR-628-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-4454	2	36	5.878	(3.033, 8.722)	< 0.001
miR-432-5p	2	324	9.815	(7.031, 12.598)	< 0.001
miR-423-5p	2	198	8.164	(3.746, 12.582)	< 0.001
miR-378	2	20	4.762	(1.863, 7.661)	0.001
miR-374b-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-30e-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-30c-5p	2	28	5.331	(2.459, 8.202)	< 0.001
miR-29c-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-29b-3p	3	114	6.588	(4.589, 8.587)	< 0.001
miR-26a-5p	3	131	6.052	(4.410, 7.694)	< 0.001
miR-23b-5p	2	36	5.883	(3.039, 8.728)	< 0.001
miR-22	2	28	5.336	(2.465, 8.207)	< 0.001
miR-208a-3p	3	100	6.412	(4.411, 8.414)	< 0.001
miR-181d-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-149-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-145-3p	4	284	6.595	(4.428, 8.762)	< 0.001
miR-143-3p	3	64	5.610	(3.589, 7.630)	< 0.001

miR-139-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-133a-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-133	2	28	5.146	(2.533, 8.279)	< 0.001
miR-132-5p	2	20	4.762	(1.863, 7.661)	0.001
miR-128-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-126-3p	2	85	7.186	(4.369, 10.004)	< 0.001
miR-125b-5p	3	46	5.519	(3.182, 7.856)	< 0.001
miR-101-5p	2	32	5.654	(2.801, 8.507)	< 0.001
miR-1-5p	7	365	7.290	(5.662, 8.919)	< 0.001
miR-26b-3p	2	28	5.352	(2.483, 8.221)	< 0.001

Supplementary Table 7. Inconsistently dysregulated miRNAs classified by different subgroups.

Subgroup	blood		tissue	
	No. of samples	expression	No. of samples	expression
miR-99a-5p	100	up	28	down
miR-9	224	up	36	down
miR-375	2312	down	8	up
miR-374a	224	up	18	down
miR-133b	195	up	28	down
miR-331-3p	2338	up	10	down
Subgroup	**Asian**		**non-Asian**	
	No. of samples	**expression**	**No. of samples**	**expression**
miR-93	11	down	28	up
miR-590-5p	18	down	28	up
miR-377	18	down	10	up
miR-25	11	down	28	up
miR-24-1	8	up	10	down

miR-152	224	up	2292	down
miR-134	18	up	2292	down
miR-106a	10	down	28	up

Supplementary Table 8. Statistically significant dysregulated miRNAs in tissue (n= 53, 21 upregulated and 32 downregulated)

	miRNA	**No. of studies**	**No. of samples**	**logOR**	**95%CI**	***P* values**
	miR-664	2	54	5.859	(3.535, 8.183)	< 0.001
up-regulated	miR-638	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-572	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-486-5p	3	122	7.298	(5.002, 9.593)	< 0.001
	miR-483-5p	3	50	5.654	(3.320, 7.987)	< 0.001
	miR-451	2	60	6.740	(3.9183, 9.563)	< 0.001
	miR-328	2	36	5.844	(2.977, 8.692)	< 0.001
	miR-301b-3p	2	94	7.666	(4.863, 10.467)	< 0.001
	miR-223-3p	6	227	6.473	(5.056, 7.890)	< 0.001
	miR-21	3	119	5.692	(3.888, 7.497)	< 0.001
	miR-19b	2	122	7.298	(5.002, 9.593)	< 0.001
	miR-193b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-18b	2	46	6.220	(3.833, 9.056)	< 0.001
	miR-155-3p	3	112	7.085	(4.786, 9.385)	< 0.001
	miR-146b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-144-5p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-142-3p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-1308	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-1202	3	50	2.869	(1.309, 4.429)	< 0.001

	miR-106b-3p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-6767-5p	2	16	4.394	(1.473, 7.316)	0.003
	miR-9	2	36	5.889	(3.045, 8.733)	< 0.001
down-regulated	miR-628-5p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-484	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-4454	2	36	5.878	(3.033, 8.722)	< 0.001
	miR-378	2	20	4.762	(1.863, 7.661)	0.001
	miR-374b-3p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-340	2	36	5.889	(3.045, 8.733)	< 0.001
	miR-30e-3p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-301a	3	40	6.081	(3.243, 8.918)	< 0.001
	miR-29c-5p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-29b-3p	2	67	6.220	(3.905, 8.535)	< 0.001
	miR-26b-3p	2	28	5.352	(2.483, 8.221)	< 0.001
	miR-26a-5p	2	83	5.692	(3.888, 7.497)	< 0.001
	miR-23b-5p	2	36	5.883	(3.039, 8.728)	< 0.001
	miR-22	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-208b	2	27	5.146	(2.261, 8.031)	< 0.001
	miR-208a-3p	3	100	6.412	(4.411, 8.414)	< 0.001
	miR-19a	3	40	6.081	(3.243, 8.918)	< 0.001
	miR-193a-5p	2	65	6.790	(3.967, 9.614)	< 0.001

miR-181d-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-149-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-145-3p	3	60	5.493	(3.469, 7.517)	< 0.001
miR-143-3p	3	64	5.610	(3.589, 7.630)	< 0.001
miR-139-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-133b	2	46	5.519	(3.182, 7.856)	< 0.001
miR-133a-5p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-133	2	28	5.146	(2.533, 8.279)	< 0.001
miR-132-5p	2	20	4.762	(1.863, 7.661)	0.001
miR-128-3p	2	28	5.336	(2.465, 8.207)	< 0.001
miR-125b-5p	3	46	5.519	(3.182, 7.856)	< 0.001
miR-101-5p	2	32	5.654	(2.801, 8.507)	< 0.001
miR-1-5p	5	84	6.241	(4.236, 8.246)	< 0.001

Supplementary Table 9. Statistically significant dysregulated miRNAs in blood (n= 7, 2 upregulated and 5 downregulated)

	miRNA	**No. of samples**	**No. of samples**	**logOR**	**95%CI**	***P* values**
up-regulated	miR-328	4	2471	8.841	(5.239, 12.443)	< 0.001
	miR-133b	2	195	8.139	(3.666, 12.612)	< 0.001
down-regulated	miR-432-5p	2	324	9.815	(7.031, 12.598)	< 0.001
	miR-375	2	2312	9.933	(2.422, 17.444)	0.010
	miR-21	2	86	6.467	(4.152, 8.783)	< 0.001
	miR-150	2	61	6.754	(3.932, 9.576)	< 0.001
	miR-1-5p	2	315	9.318	(6.331, 12.306)	< 0.001

Supplementary Table 10. Statistically significant dysregulated miRNAs in microarray studies (n=12, 6 upregulated and 6 downregulated)

	miRNA	**No. of studies**	**No. of samples**	**logOR**	**95%CI**	***P* values**
up-regulated	miR-638	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-572	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-483-5p	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-223-3p	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-193b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-1202	3	50	2.869	(1.309, 4.429)	< 0.001
down-regulated	miR-99a	2	36	5.889	(3.045, 8.733)	< 0.001
	miR-9	2	36	5.889	(3.045, 8.733)	< 0.001
	miR-340	2	36	5.889	(3.045, 8.733)	< 0.001
	miR-301a	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-29b-3p	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-19a	2	40	6.081	(3.243, 8.918)	< 0.001

SupplementaryTable 11. Statistically significant dysregulated miRNAs in qRT-PCR studies (n= 29, 15 upregulated and 14 downregulated)

	miRNA	**No. of studies**	**No. of samples**	**logOR**	**95%CI**	***P* values**
	miR-664	2	36	5.844	(2.977, 8.692)	< 0.001
up-regulated	miR-486-5p	3	122	7.298	(5.002, 9.593)	< 0.001
	miR-451	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-328	5	2507	7.851	(5.236, 10.466)	< 0.001
	miR-301b-3p	2	94	7.666	(4.863, 10.467)	< 0.001
	miR-223-3p	6	227	6.603	(4.967, 8.238)	< 0.001
	miR-21	3	150	6.750	(4.877, 8.866)	< 0.001
	miR-19b	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-19a	2	48	6.319	(3.486, 9.152)	< 0.001
	miR-192-5p	2	106	6.611	(1.380, 11.841)	0.013
	miR-155-3p	2	94	7.666	(4.863, 10.469)	< 0.001
	mIR-146b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-144-5p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-142-3p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-106b-3p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-4454	2	36	5.878	(3.033, 8.722)	< 0.001
down-regulated	miR-378	2	20	4.762	(1.863, 7.661)	0.001

miR-375	2	2312	9.933	(2.422, 17.444)	0.010
miR-30c-5p	2	28	5.331	(2.459, 8.202)	< 0.001
miR-29b-3p	2	64	7.087	(4.271, 9.903)	< 0.001
miR-26a-5p	3	113	6.085	(4.286, 7.884)	< 0.001
miR-150	2	61	6.754	(3.932, 9.576)	< 0.001
miR-145-3p	2	24	5.093	(2.213, 7.974)	0.001
miR-143-3p	2	46	5.515	(3.178, 7.852)	< 0.001
miR-133b	3	28	5.331	(2.459, 8.202)	< 0.001
miR-133	2	28	5.146	(2.533, 8.279)	< 0.001
miR-132-5p	2	20	4.762	(1.863, 7.661)	0.001
miR-126b-5p	2	28	2.620	(0.729, 4.511)	0.007
miR-1-5p	5	141	6.55	(4.767, 8.345)	< 0.001

Supplementary Table 12. Statistically significant dysregulated miRNAs in Asian countries (n=31, 15 upregulated and 16 downregulated)

	miRNA	**No. of studies**	**No. of samples**	**logOR**	**95%CI**	***P* values**
	miR-664	2	278	7.131	(4.642, 9.620)	< 0.001
up-regulated	miR-486-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-454-5p	2	232	7.646	(1.338, 13.955)	0.018
	miR-328	3	149	6.774	(4.775, 8.773)	< 0.001
	miR-301b-3p	2	94	7.666	(4.863, 10.467)	< 0.001
	miR-223-3p	3	195	6.777	(5.146, 8.407)	< 0.001
	miR-21	2	68	6.860	(4.035, 9.684)	< 0.001
	miR-208b-3p	2	27	5.146	(2.261, 8.031)	< 0.001
	miR-19b	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-193b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-192-5p	2	106	6.611	(1.380, 11.841)	0.013
	miR-155-3p	3	112	7.085	(4.786, 9.385)	< 0.001
	mIR-146b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-143	2	54	5.881	(3.559, 8.204)	< 0.001
	miR-142-3p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-99a	2	36	5.889	(3.045, 8.733)	< 0.001
down-regulated	miR-9	2	36	5.889	(3.045, 8.733)	< 0.001
	miR-4454	2	36	5.878	(3.033, 8.722)	< 0.001
	miR-432-5p	2	324	9.815	(7.031, 12.598)	< 0.001

miR-423-5p	2	198	8.164	(3.746, 12.582)	< 0.001
miR-340	2	36	5.889	(3.045, 8.733)	< 0.001
miR-26b-3p	2	28	5.352	(2.483, 8.221)	< 0.001
miR-26a-5p	3	83	5.692	(3.888, 7.497)	< 0.001
miR-193a-5p	2	65	6.790	(3.967, 9.614)	< 0.001
miR-150	2	61	6.754	(3.932, 9.576)	< 0.001
miR-145-3p	3	256	7.408	(3.984, 10.831)	< 0.001
miR-133b	2	36	5.883	(3.039, 8.728)	< 0.001
miR-133	2	28	5.146	(2.533, 8.279)	< 0.001
miR-132-5p	2	20	4.762	(1.863, 7.661)	0.001
miR-126-3p	2	85	7.186	(4.369, 10.004)	< 0.001
miR-1-5p	3	282	8.067	(5.191, 10.943)	< 0.001

Supplementary Table 13. Statistically significant dysregulated miRNAs in non-Asian countries (n=14, 8 upregulated and 6 downregulated)

	miRNA	No. of studies	No. of samples	logOR	95%CI	*P* values
up-regulated	miR-451	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-483-5p	2	32	5.534	(2.670, 8.399)	< 0.001
	miR-328	2	2499	9.985	(1.873, 18.097)	< 0.001
	miR-223-3p	2	32	5.534	(2.670, 8.399)	< 0.001
	miR-21	2	62	6.882	(4.066, 9.699)	< 0.001
	miR-150	2	2391	9.101	(4.139, 14.062)	< 0.001
	miR-1202	2	32	5.534	(2.670, 8.399)	< 0.001
	miR-106b-3p	2	60	6.740	(3.918, 9.563)	< 0.001
down-regulated	miR-378	2	20	4.762	(1.863, 7.661)	0.001
	miR-29b-3p	2	106	6.817	(4.513, 9.121)	< 0.001
	miR-208a-3p	2	82	6.585	(4.278, 8.892)	< 0.001
	miR-144	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-101	2	32	5.654	(2.801, 8.507)	< 0.001
	miR-1-5p	4	83	6.487	(4.176, 8.799)	< 0.001

Supplementary Table 14. The dysregulation of miRNAs in animals' model (n=10, 3 upregulated and 7 downregulated)

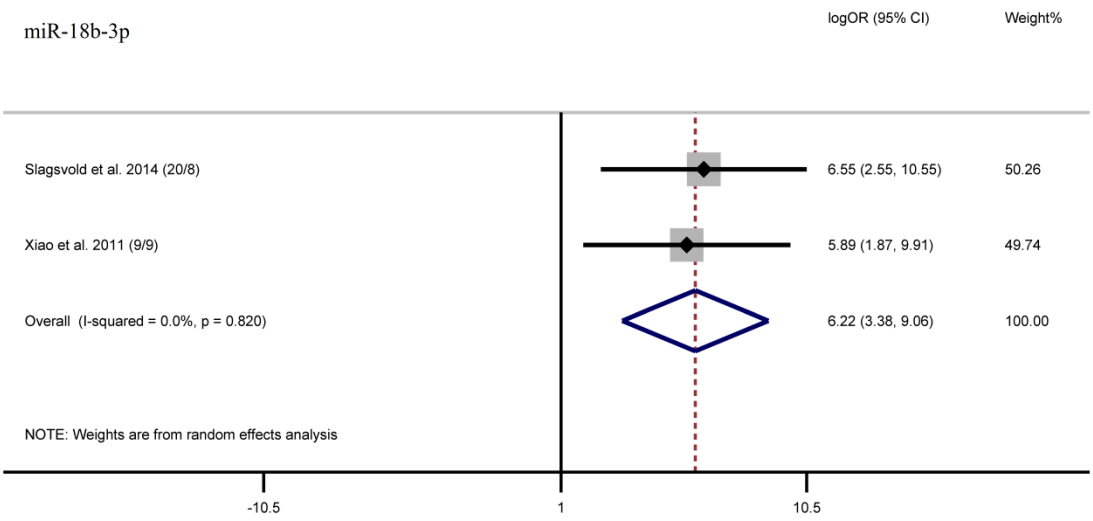
	miRNA	**No. of studies**	**No. of samples**	**logOR**	**95%CI**	***P* values**
up-regulated	miR-664	1	14	-	-	-
	miR-328	1	14	-	-	-
	miR-31	1	18	-	-	-
down-regulated	miR-499	1	14	-	-	-
	miR-320	1	14	-	-	-
	miR-30	1	14	-	-	-
	miR-26a-5p	1	19	-	-	-
	miR-145	1	14	-	-	-
	miR-133	2	28	5.1460	(2.533, 8.279)	< 0.001
	miR-101	1	14	-	-	-

Supplementary Table 15. Statistically significant dysregulated miRNAs in sensitivity analysis according to sample sizes (n= 47, 18 upregulated and 29 downregulated)

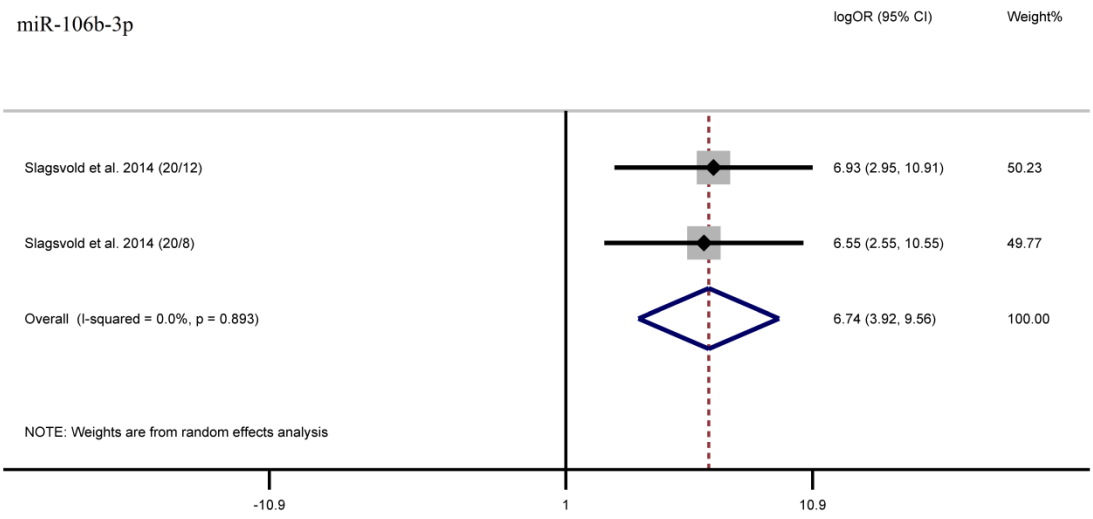
	miRNA	No. of studies	No. of samples	logOR	95%CI	*P* values
up-regulated	miR-664	2	278	7.131	(4.642, 9.620)	< 0.001
	miR-638	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-572	2	40	6.081	(3.243, 8.918)	< 0.001
	miR-486-5p	2	122	7.298	(5.002, 9.593)	< 0.001
	miR-483-5p	3	50	5.654	(3.320, 7.987)	< 0.001
	miR-301b-3p	2	94	7.666	(4.863, 10.467)	< 0.001
	miR-223-3p	6	227	6.473	(5.056, 7.890)	< 0.001
	miR-193b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-18b-3p	2	46	6.220	(3.833, 9.056)	< 0.001
	miR-155-3p	3	112	7.085	(4.786, 9.385)	< 0.001
	miR-146b-5p	2	94	7.666	(4.863, 10.469)	< 0.001
	miR-146	2	234	7.827	(1.878, 13.775)	0.010
	miR-144-5p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-1308	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-1202	3	50	2.869	(1.309, 4.429)	< 0.001
	miR-106b-3p	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-142-3p	2	94	7.666	(4.863, 10.469)	< 0.001

	miR-451a	2	60	6.740	(3.918, 9.563)	< 0.001
	miR-484	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-628-5p	2	28	5.336	(2.465, 8.207)	< 0.001
down-regulated	miR-4454	2	36	5.878	(3.033, 8.722)	< 0.001
	miR-432-5p	2	324	9.815	(7.031, 12.598)	< 0.001
	miR-423-5p	2	198	8.164	(3.746, 12.582)	< 0.001
	miR-378	2	20	4.762	(1.863, 7.661)	0.001
	miR-374b-3p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-30e-3p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-30c-5p	2	28	5.331	(2.459, 8.202)	< 0.001
	miR-29c-5p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-29b-3p	3	114	6.588	(4.589, 8.587)	< 0.001
	miR-26a-5p	3	131	6.052	(4.410, 7.694)	< 0.001
	miR-23b-5p	2	36	5.883	(3.039, 8.728)	< 0.001
	miR-22	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-208a-3p	3	100	6.412	(4.411, 8.414)	< 0.001
	miR-181d-3p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-149-5p	2	28	5.336	(2.465, 8.207)	< 0.001
	miR-145-3p	4	284	6.595	(4.428, 8.762)	< 0.001
	miR-143-3p	3	64	5.610	(3.589, 7.630)	< 0.001
	miR-139-5p	2	28	5.336	(2.465, 8.207)	< 0.001

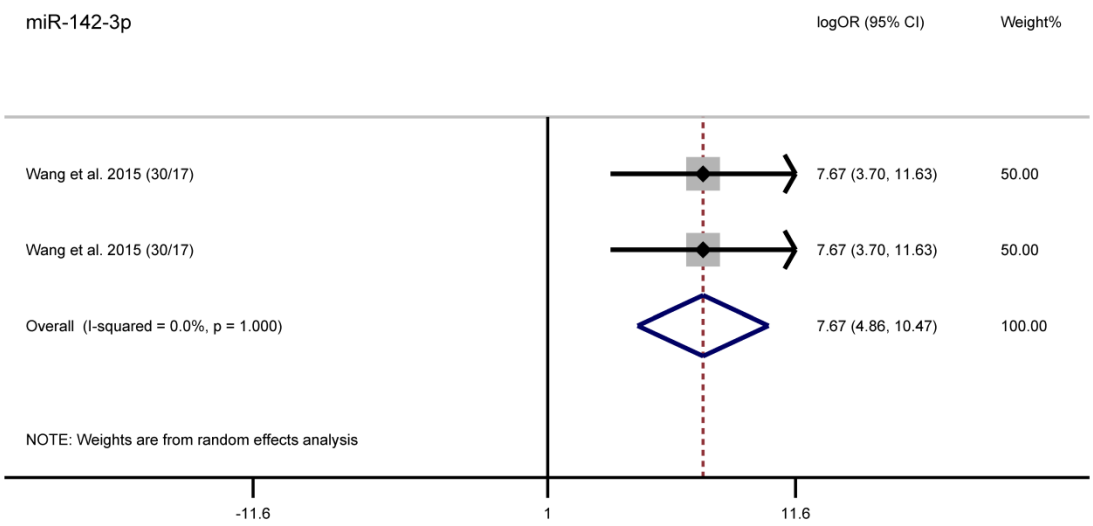
	miR-133a-5p	2	28	5.3360	(2.465, 8.207)	< 0.001
	miR-133	2	28	5.1460	(2.533, 8.279)	< 0.001
	miR-132-5p	2	20	4.7620	(1.863, 7.661)	0.001
	miR-128-3p	2	28	5.3360	(2.465, 8.207)	< 0.001
	miR-126-3p	2	85	7.1860	(4.369, 10.004)	< 0.001
	miR-125b-5p	3	46	5.5190	(3.182, 7.856)	< 0.001
	miR-101-5p	2	32	5.6540	(2.801, 8.507)	< 0.001
	miR-1-5p	7	365	7.2900	(5.662, 8.919)	< 0.001
	miR-26b-3p	2	28	5.3520	(2.483, 8.221)	< 0.001



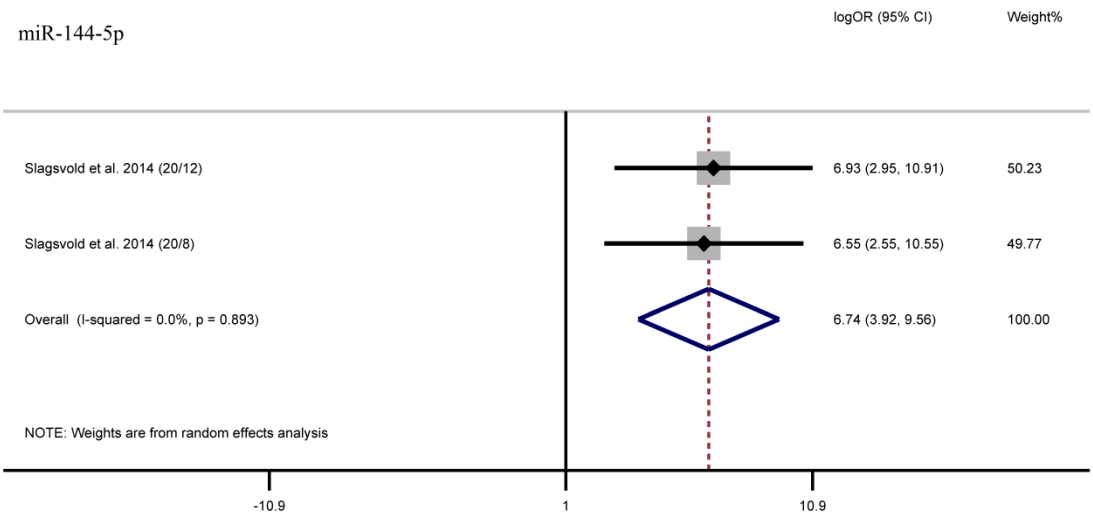
Supplementary Figure1. Forest plot of miR-18b-3p



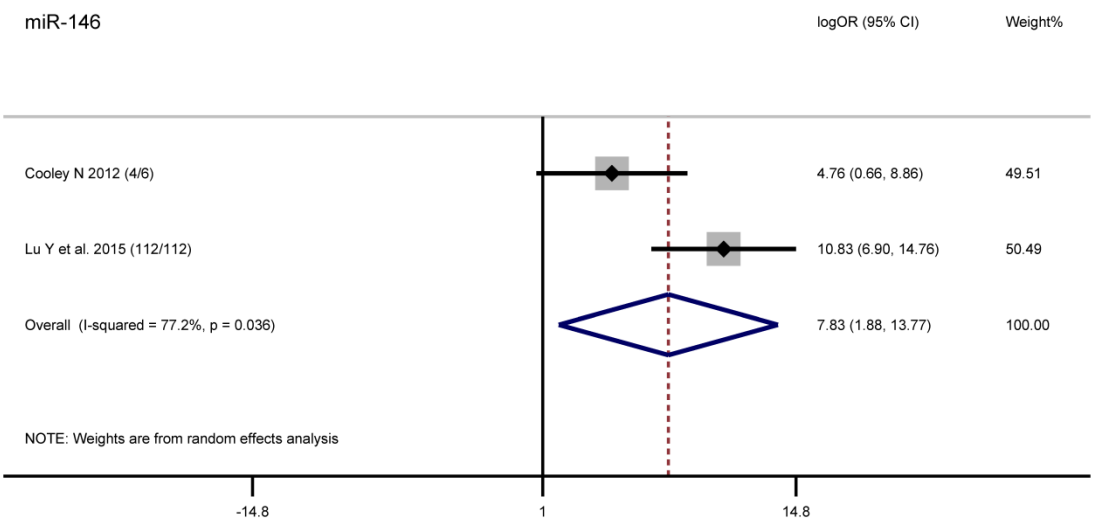
Supplementary Figure2. Forest plot of miR-106b-3p



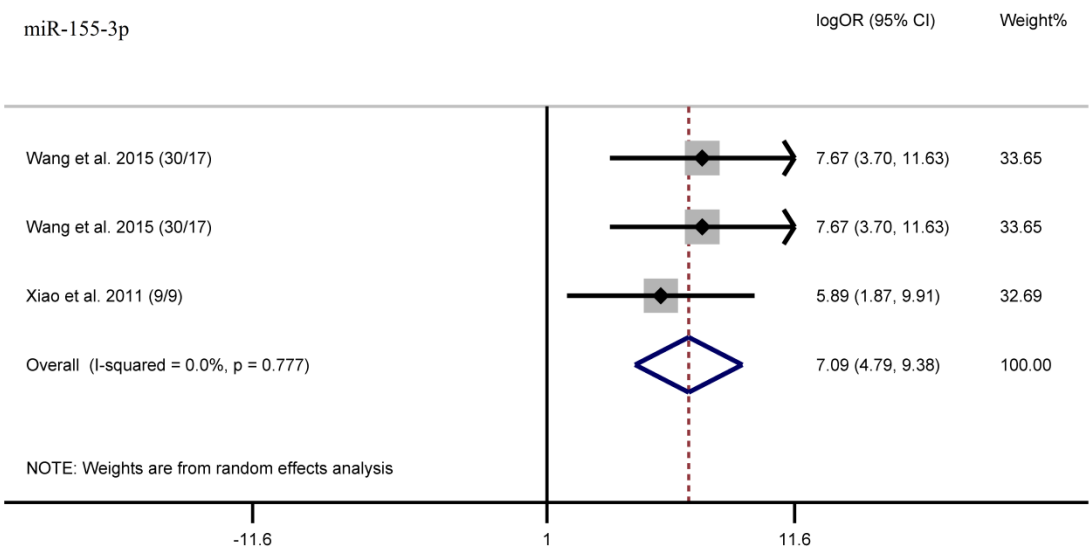
Supplementary Figure3. Forest plot of miR-142-3p



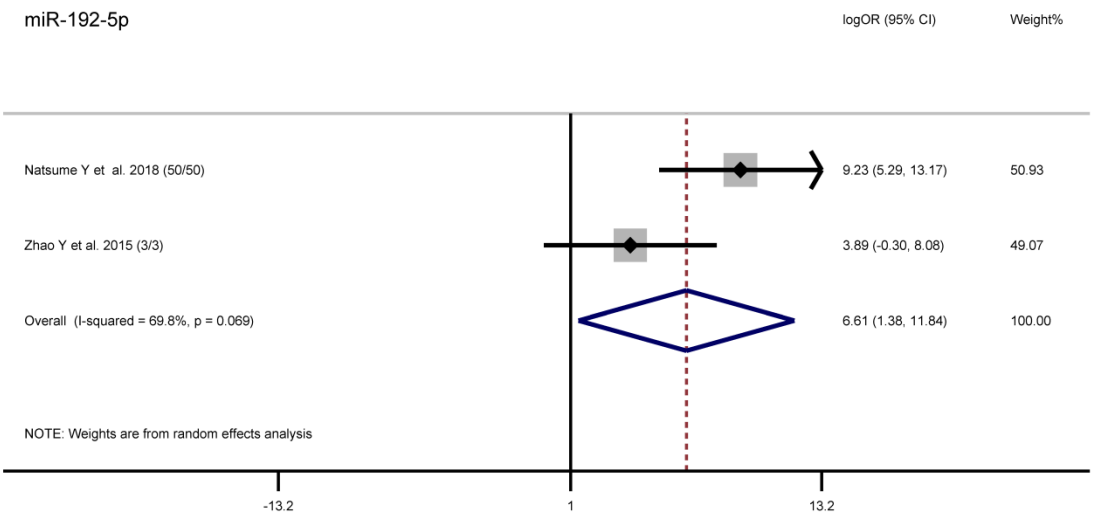
Supplementary Figure4. Forest plot of miR-144-5p



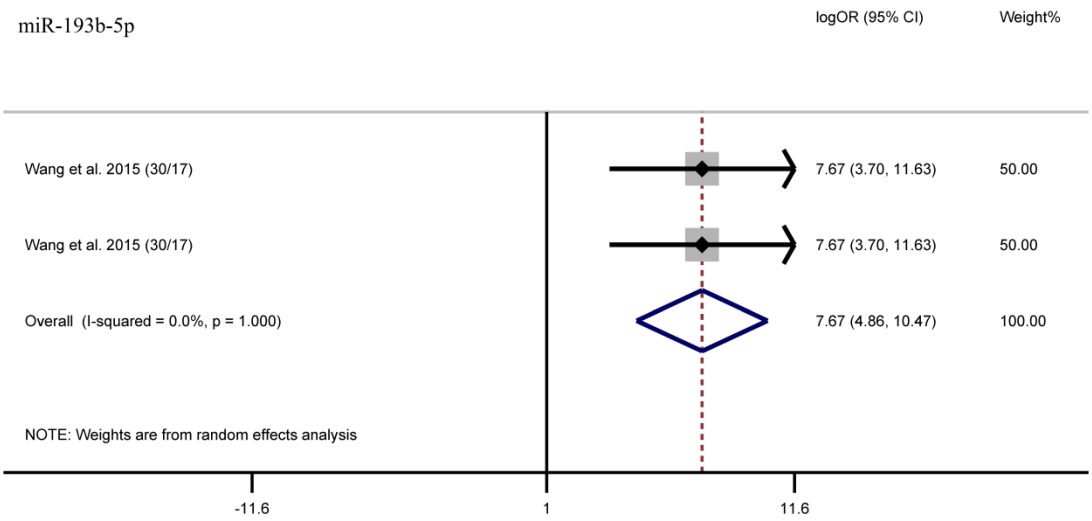
Supplementary Figure5. Forest plot of miR-146



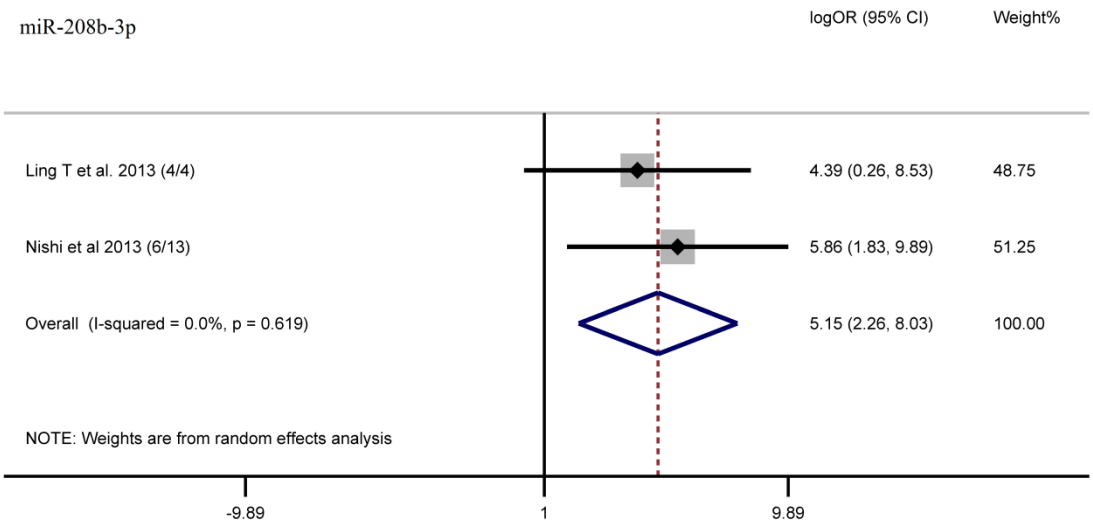
Supplementary Figure6. Forest plot of miR-155-3p



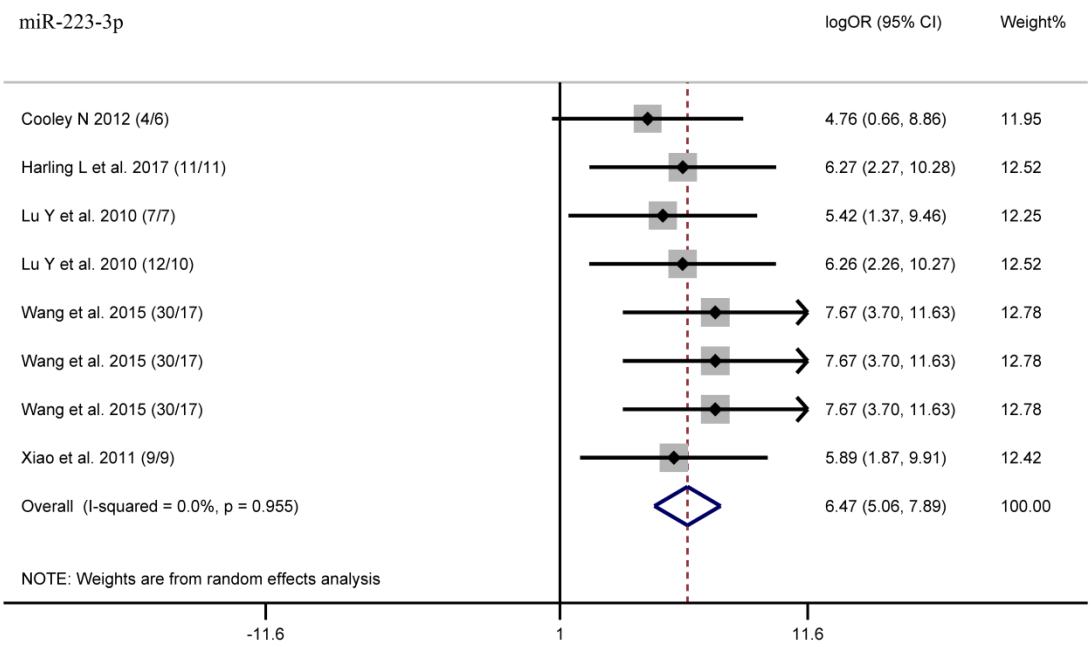
Supplementary Figure 7. Forest plot of miR-192-5p



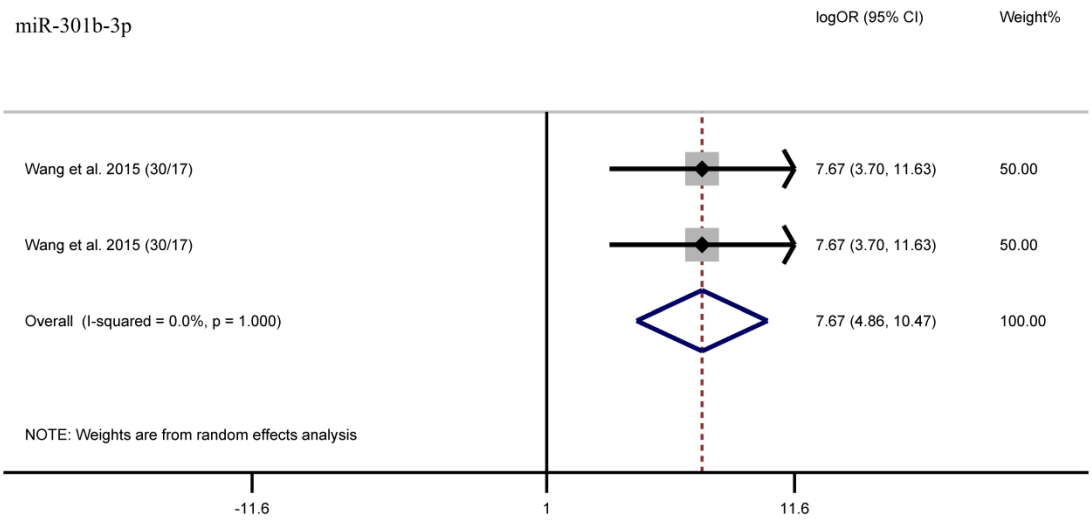
Supplementary Figure8. Forest plot of miR-193b-5p



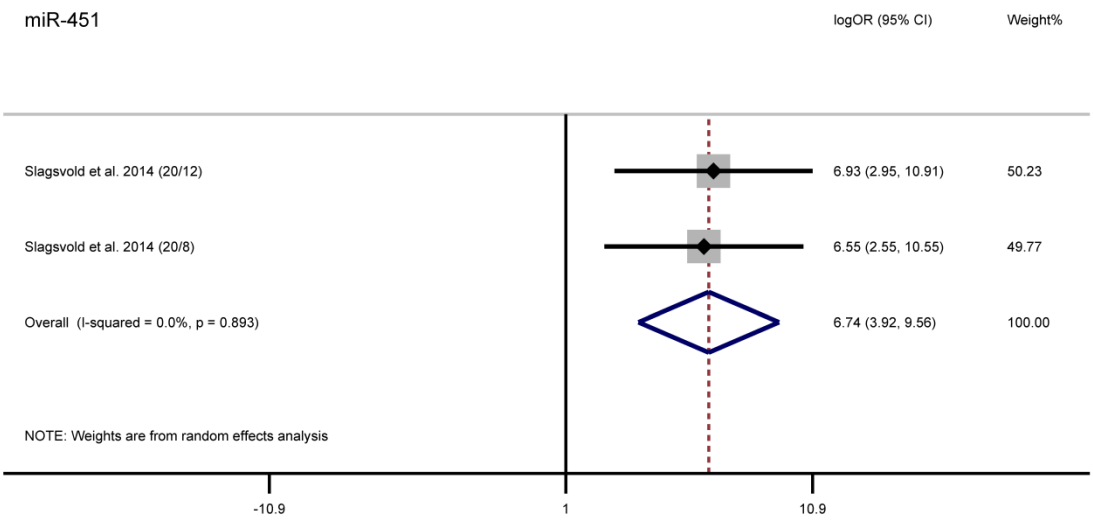
Supplementary Figure9. Forest plot of miR-208b-3p



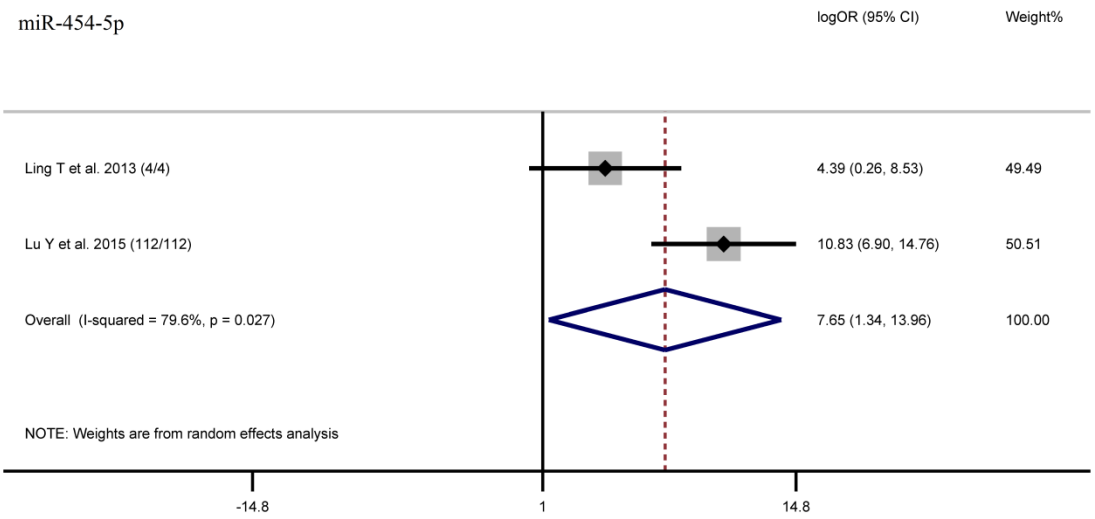
Supplementary Figure10. Forest plot of miR-223-3p



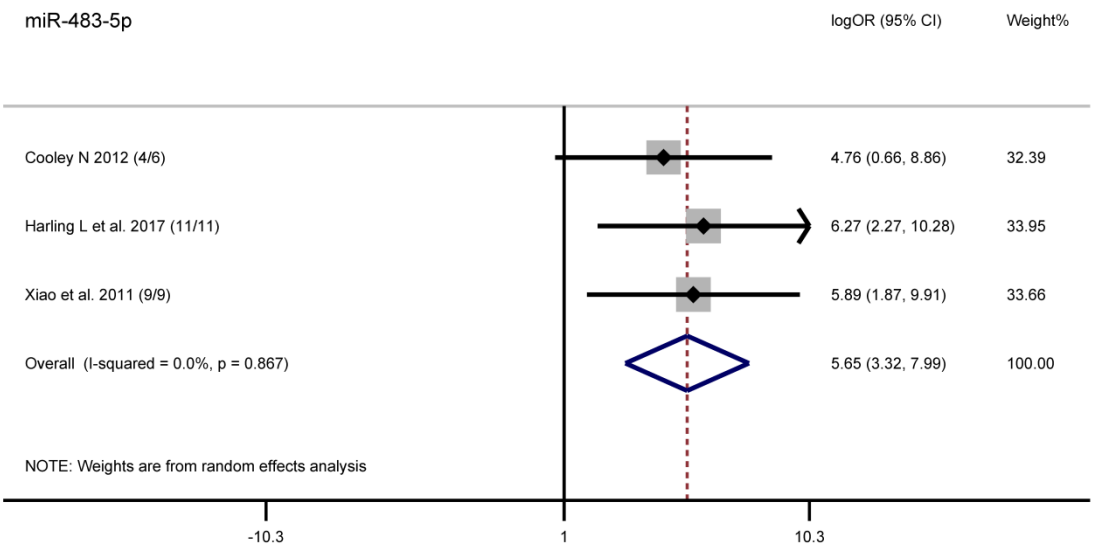
Supplementary Figure 11. Forest plot of miR-301b-3p



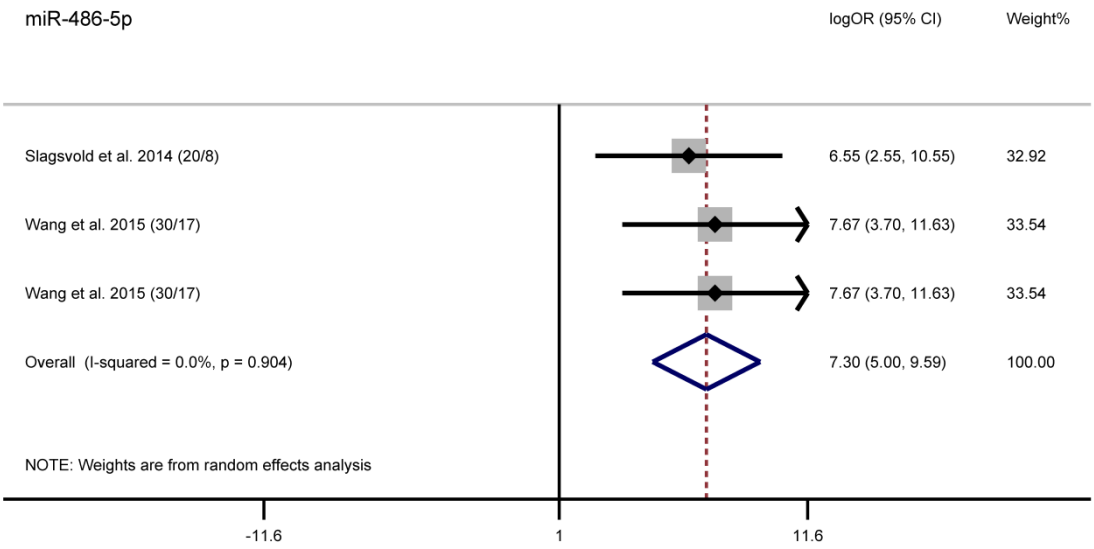
Supplementary Figure 12. Forest plot of miR-451



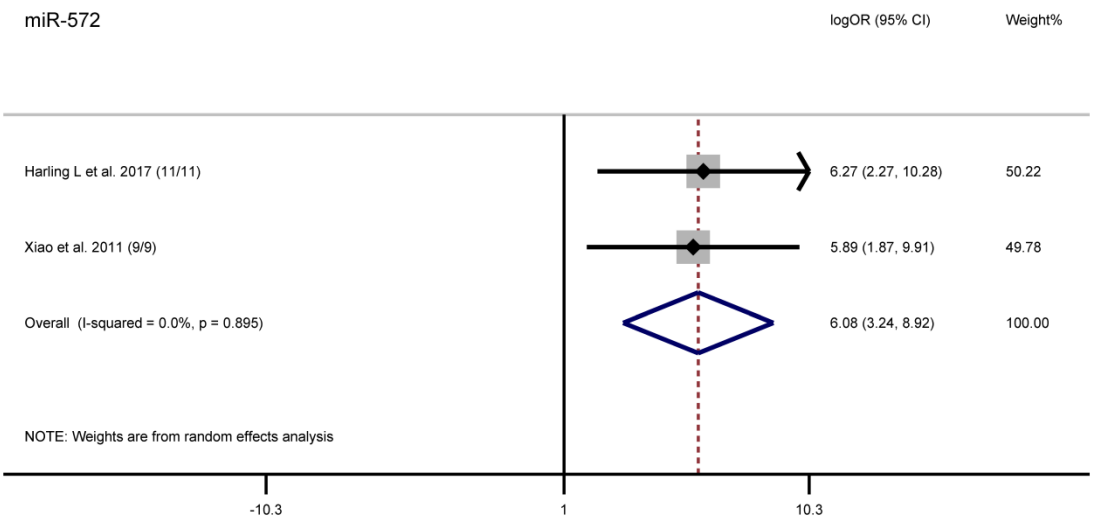
Supplementary Figure13. Forest plot of miR-454-5p



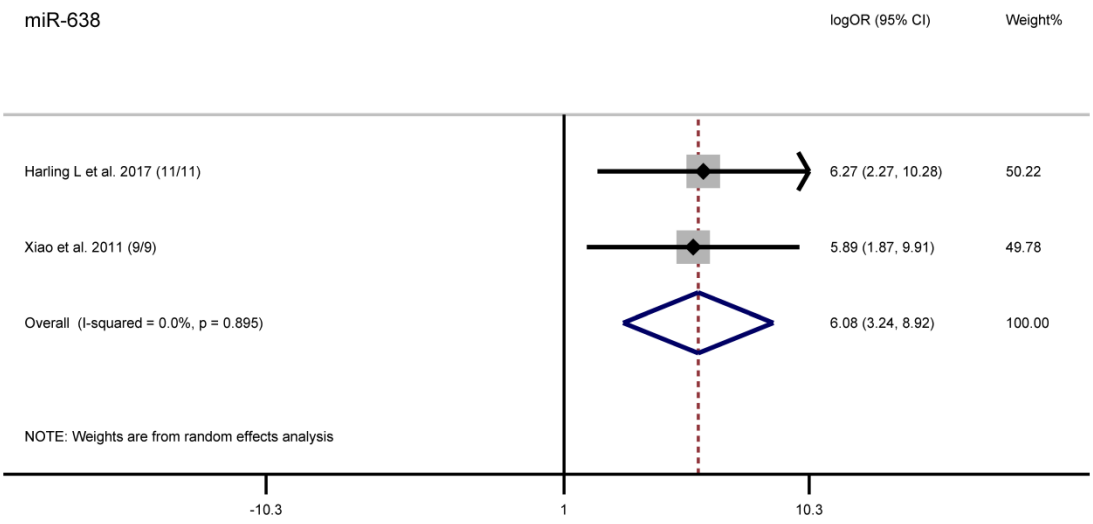
Supplementary Figure14. Forest plot of miR-483-5p



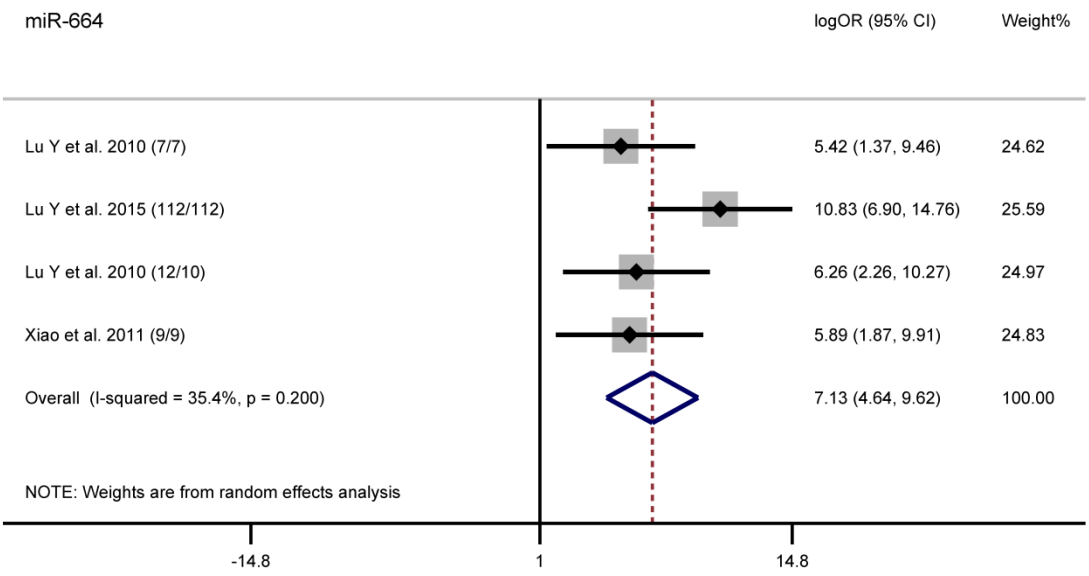
Supplementary Figure15. Forest plot of miR-486-5p



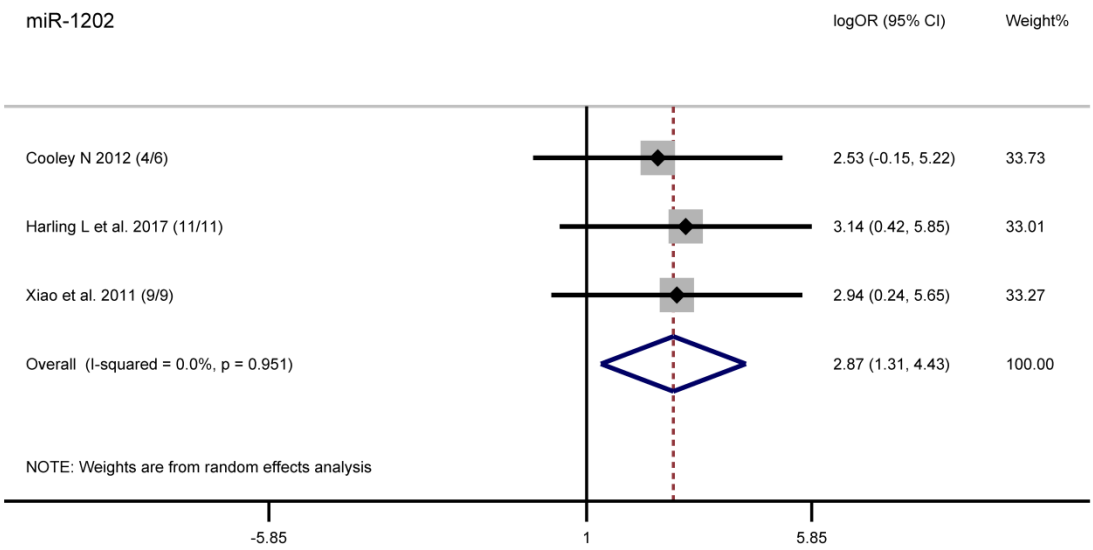
Supplementary Figure 16. Forest plot of miR-572



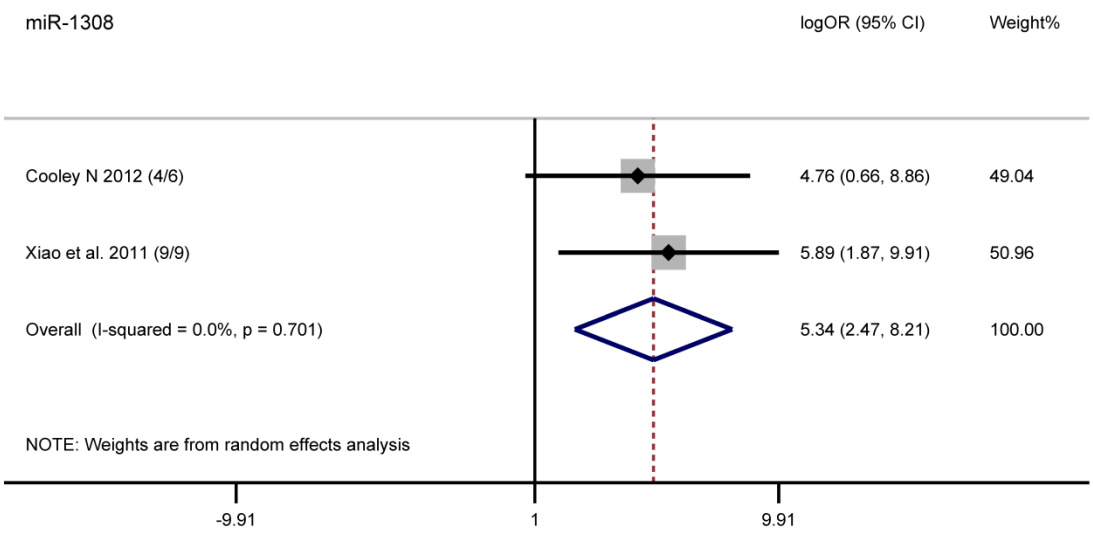
Supplementary Figure 17. Forest plot of miR-638



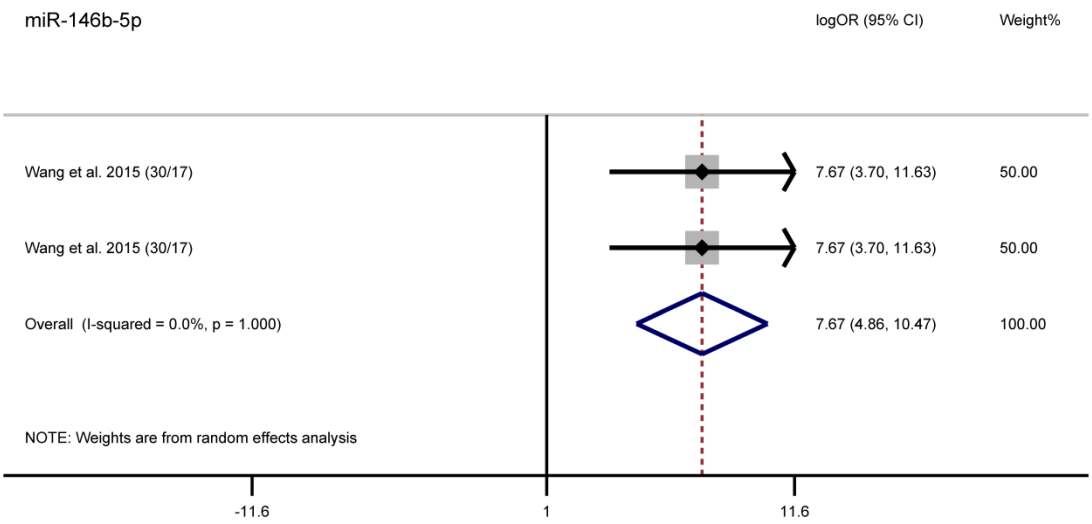
Supplementary Figure18. Forest plot of miR-664



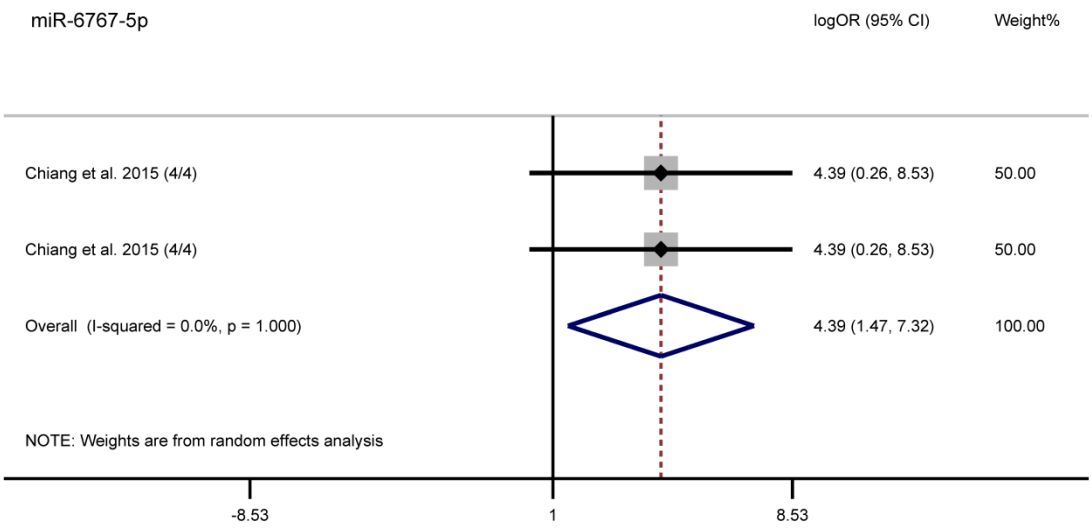
Supplementary Figure19. Forest plot of miR-1202



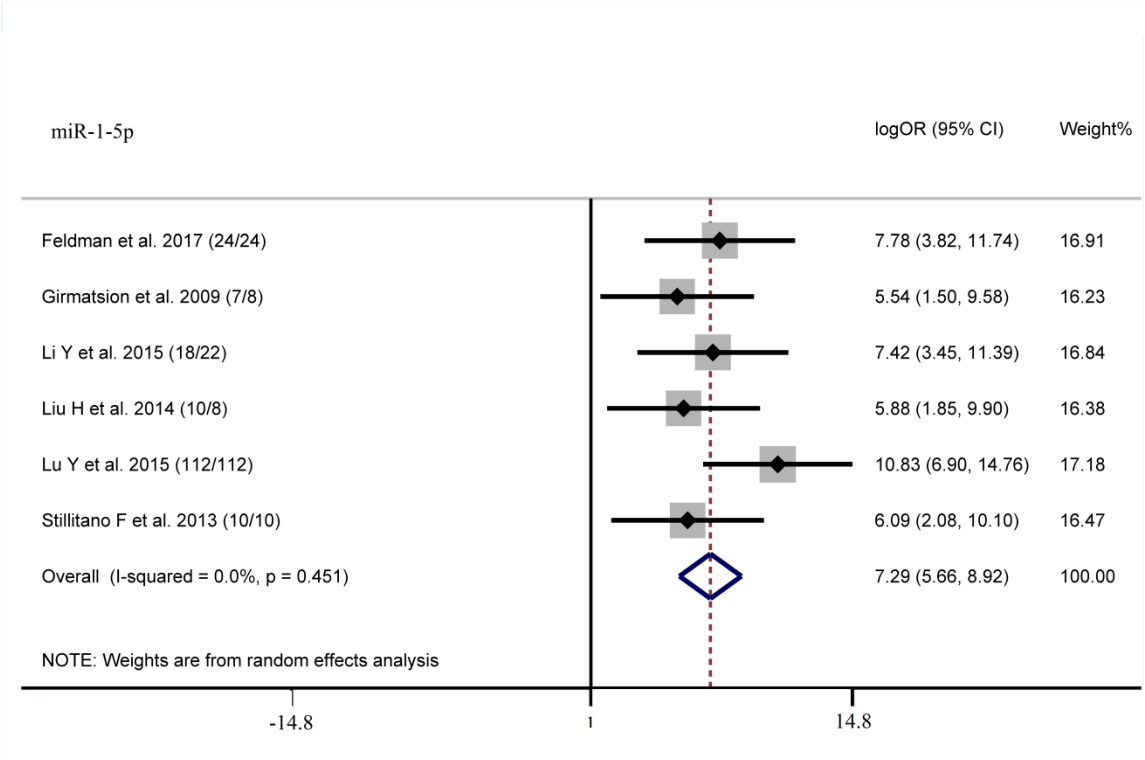
Supplementary Figure20. Forest plot of miR-1308



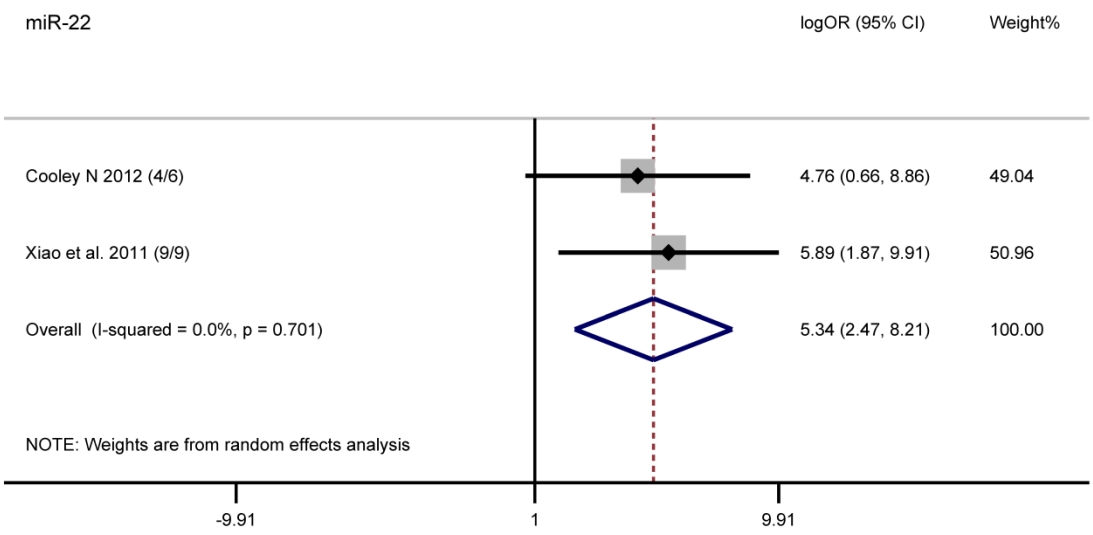
Supplementary Figure 21. Forest plot of miR-146b-5p



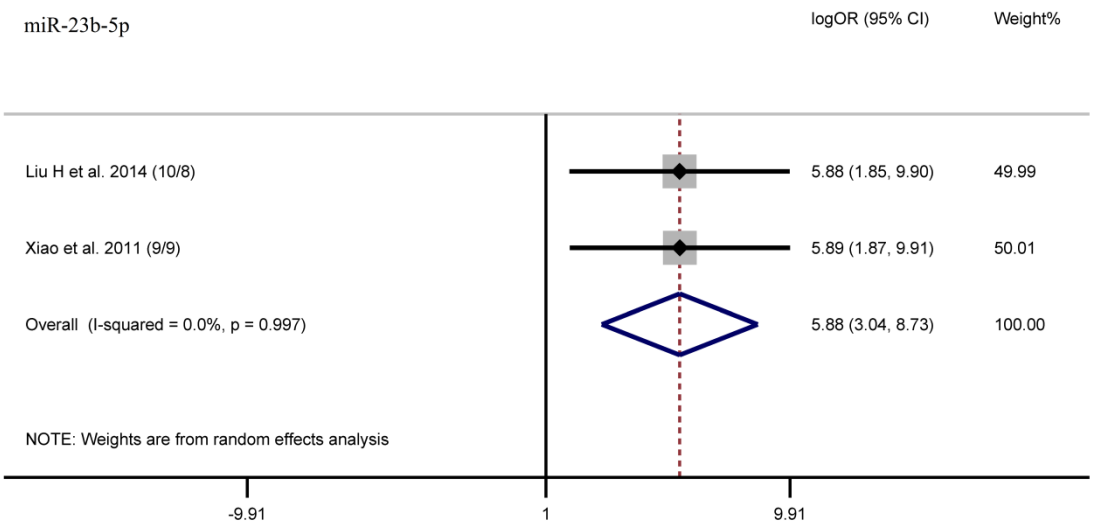
Supplementary Figure 22. Forest plot of miR-6767-5p



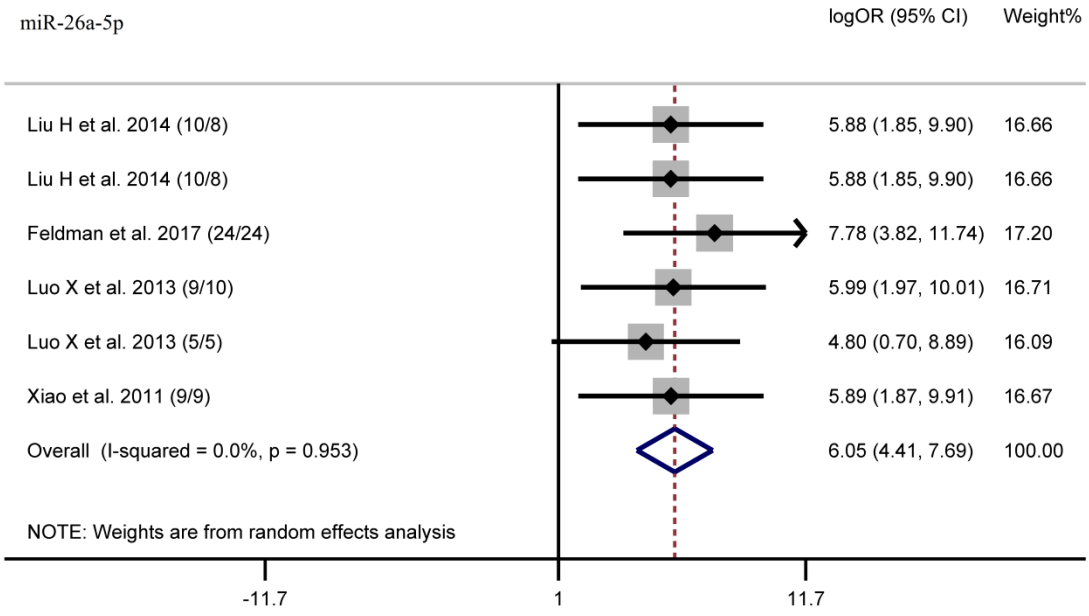
Supplementary Figure23. Forest plot of miR-1-5p



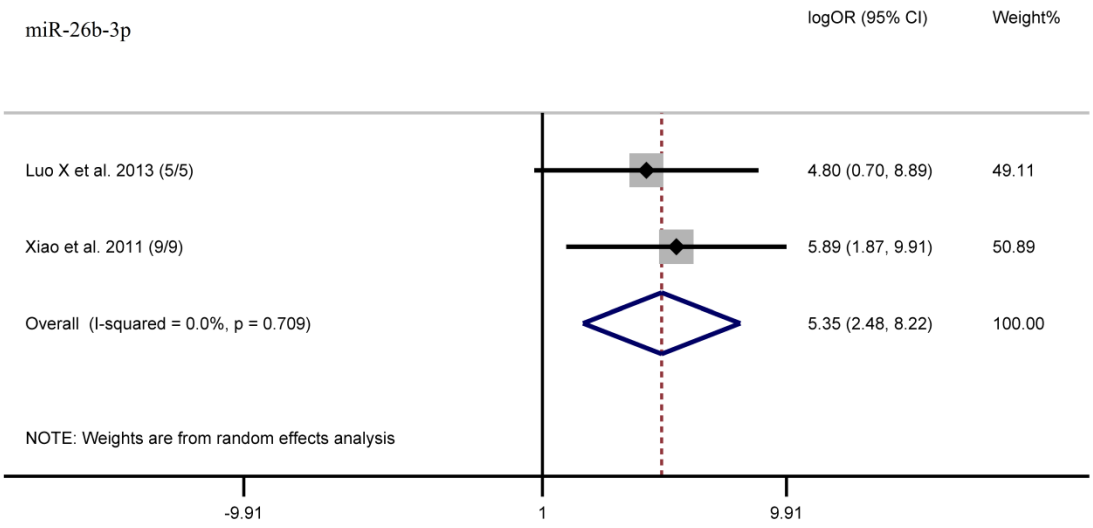
Supplementary Figure24. Forest plot of miR-22



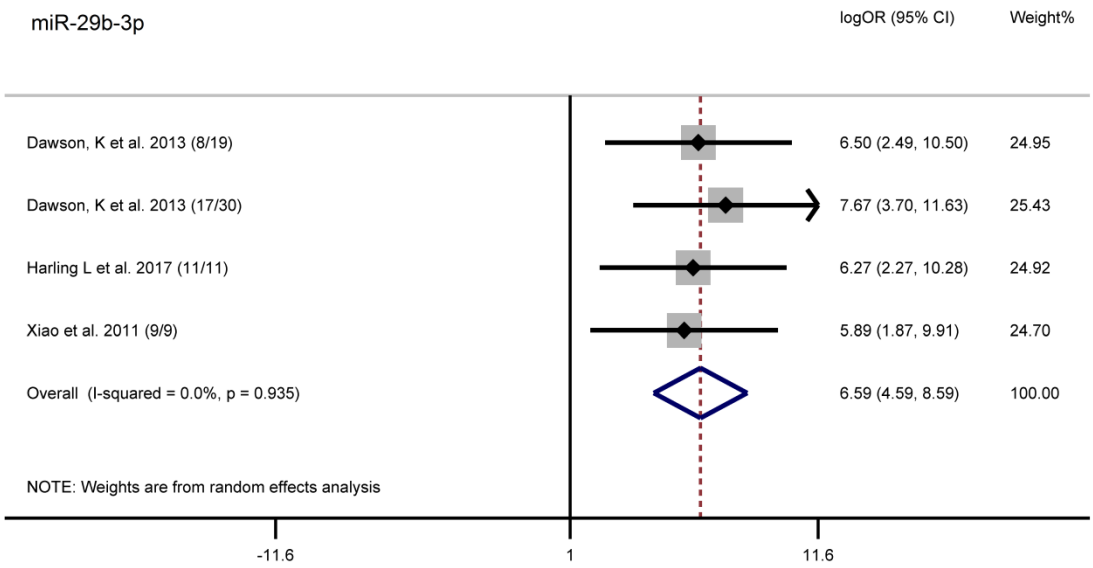
Supplementary Figure25. Forest plot of miR-23b-5p



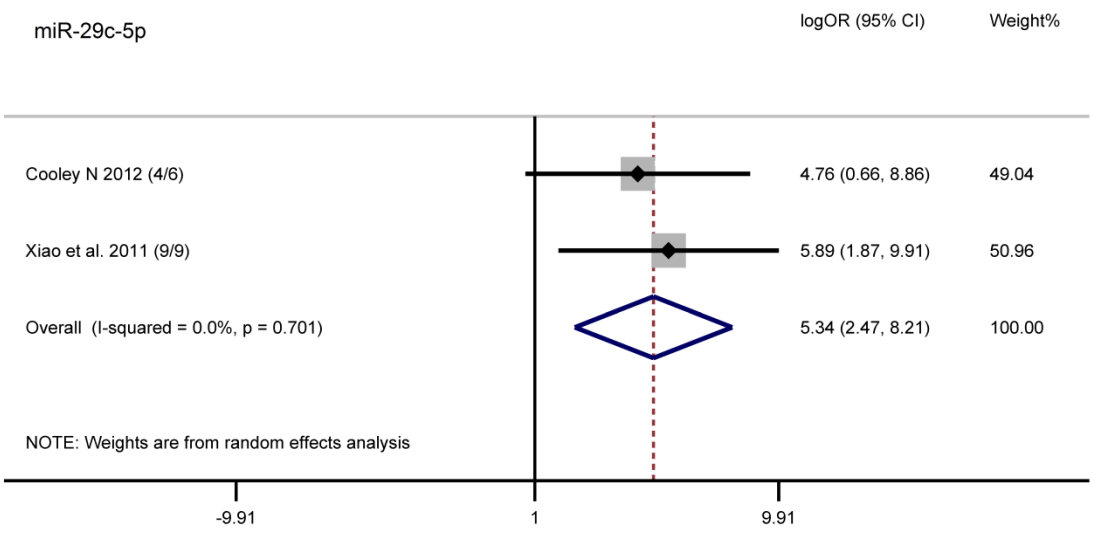
Supplementary Figure26. Forest plot of miR-26a-5p



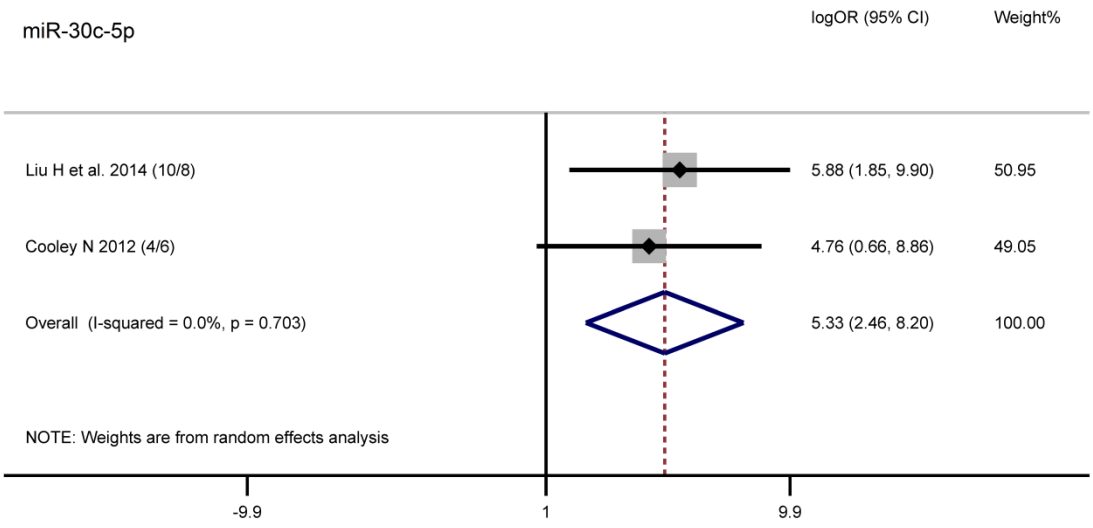
Supplementary Figure27. Forest plot of miR-26b-3p



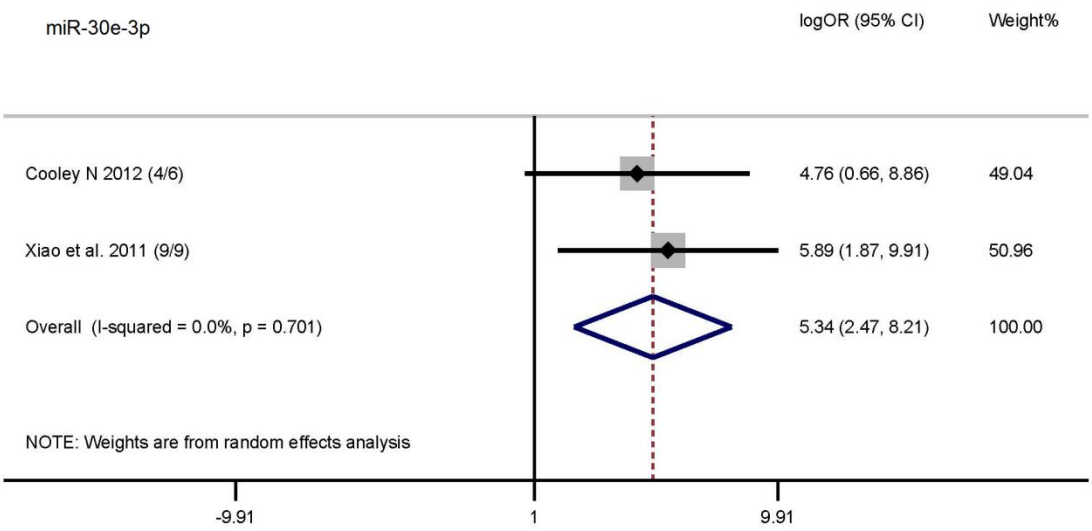
Supplementary Figure28. Forest plot of miR-29b-3p



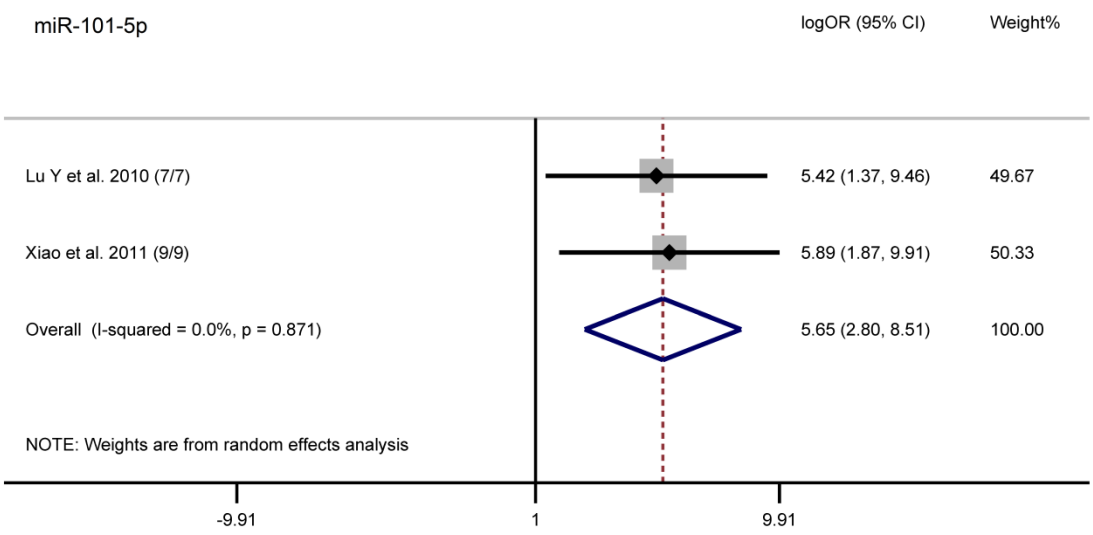
Supplementary Figure 29. Forest plot of miR-29c-5p



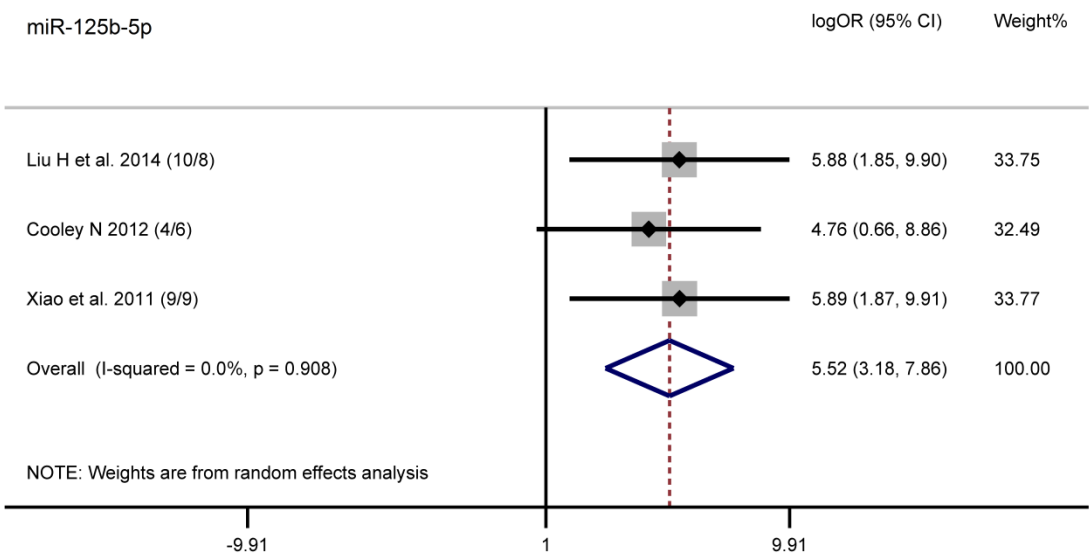
Supplementary Figure30. Forest plot of miR-30c-5p



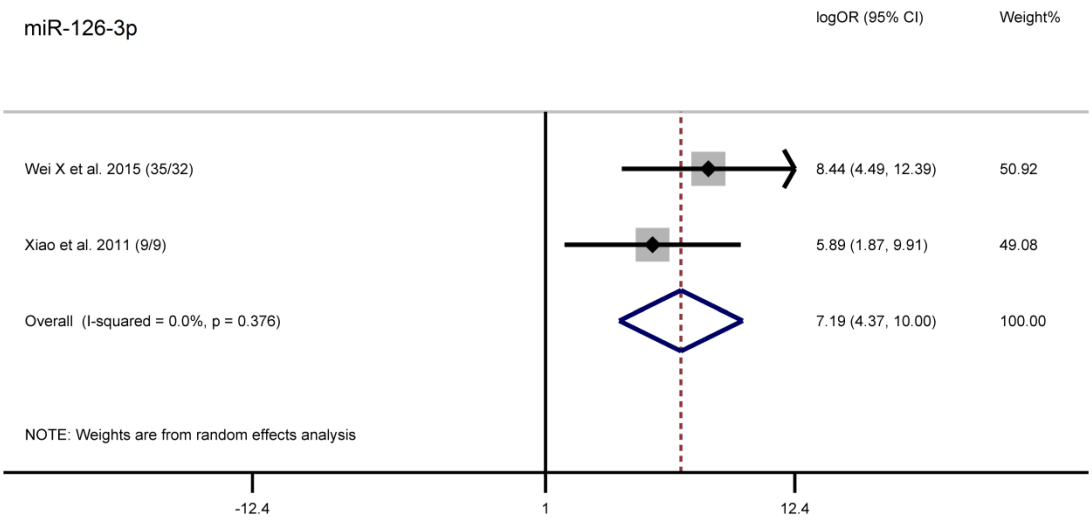
Supplementary Figure31. Forest plot of miR-30e-3p



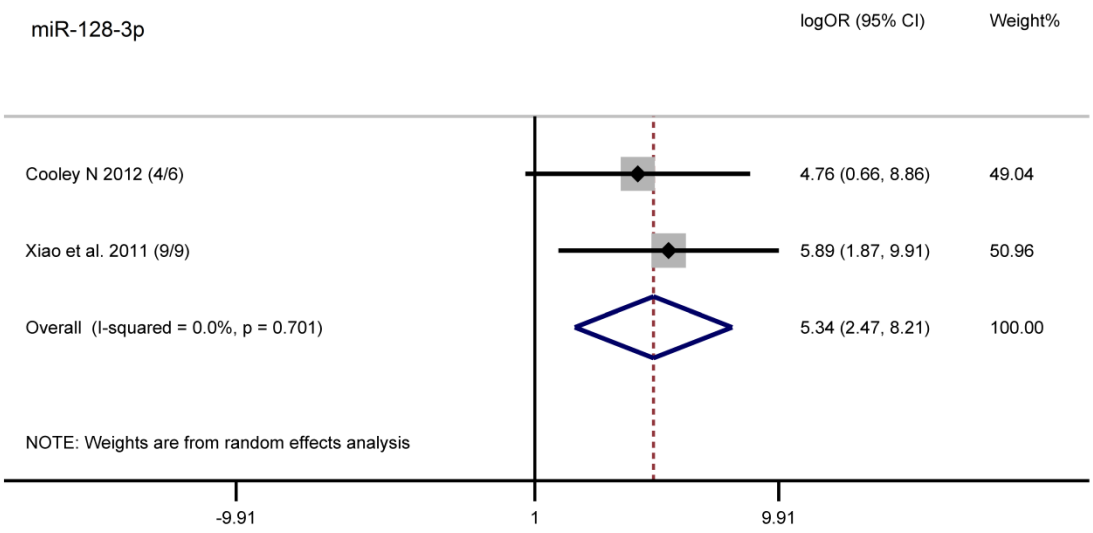
Supplementary Figure32. Forest plot of miR-101-5p



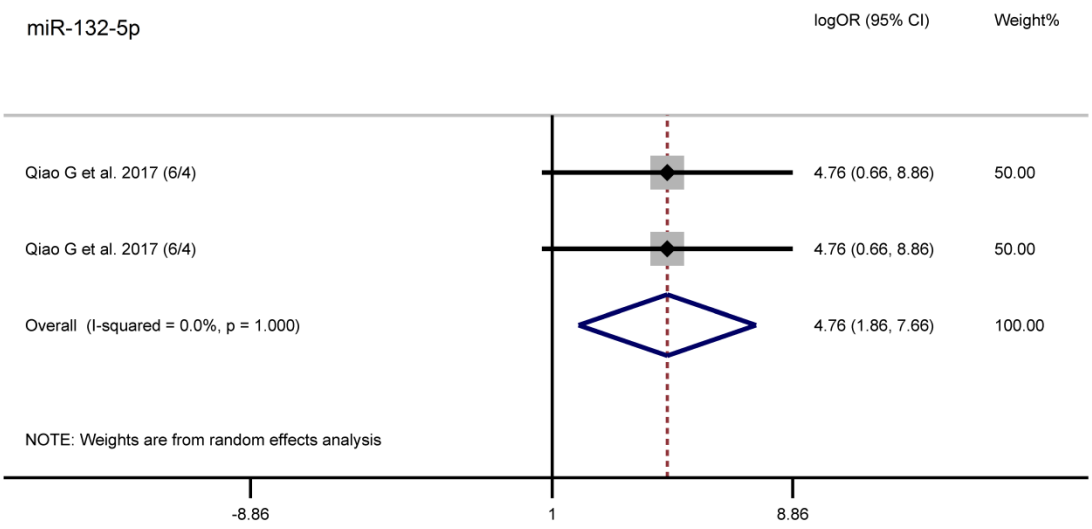
Supplementary Figure 33. Forest plot of miR-125b-5p



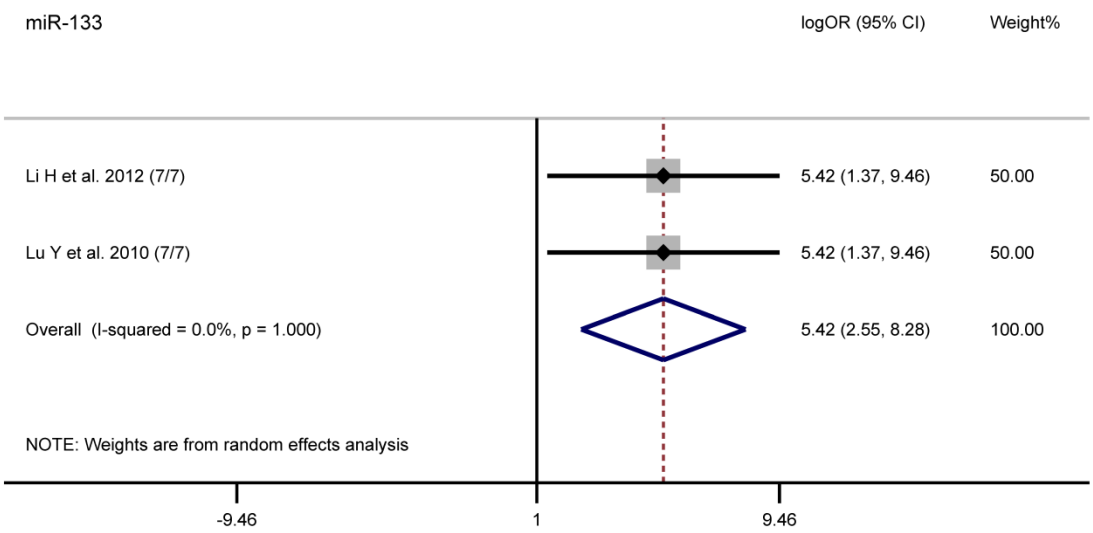
Supplementary Figure34. Forest plot of miR-126-3p



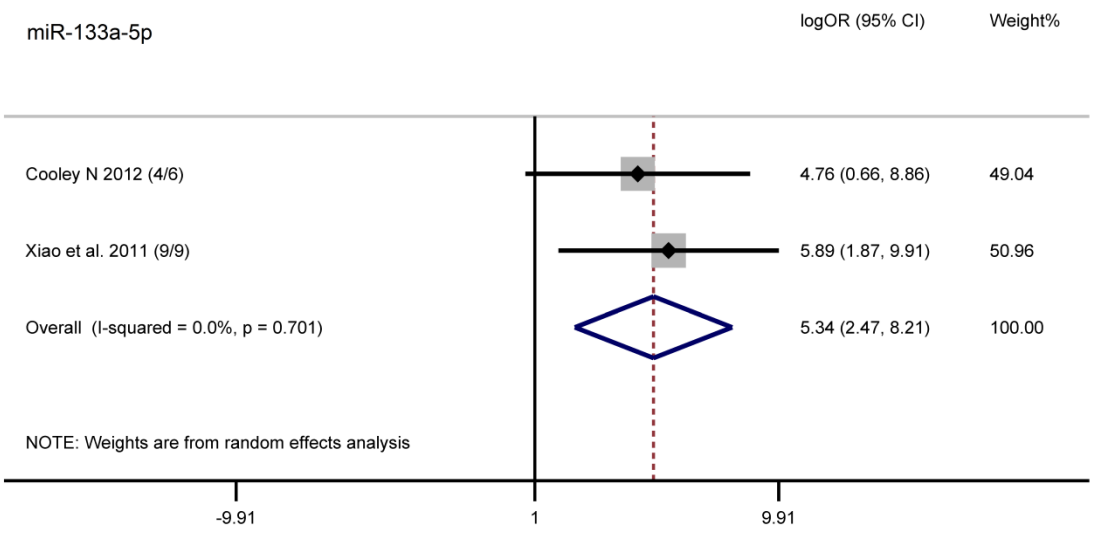
Supplementary Figure35. Forest plot of miR-128-3p



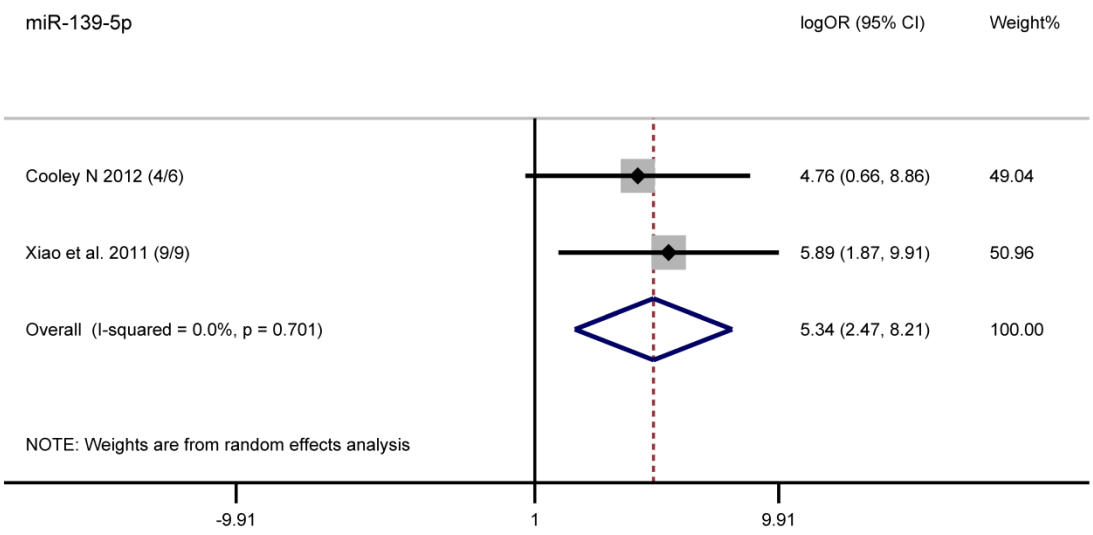
Supplementary Figure36. Forest plot of miR-132-5p



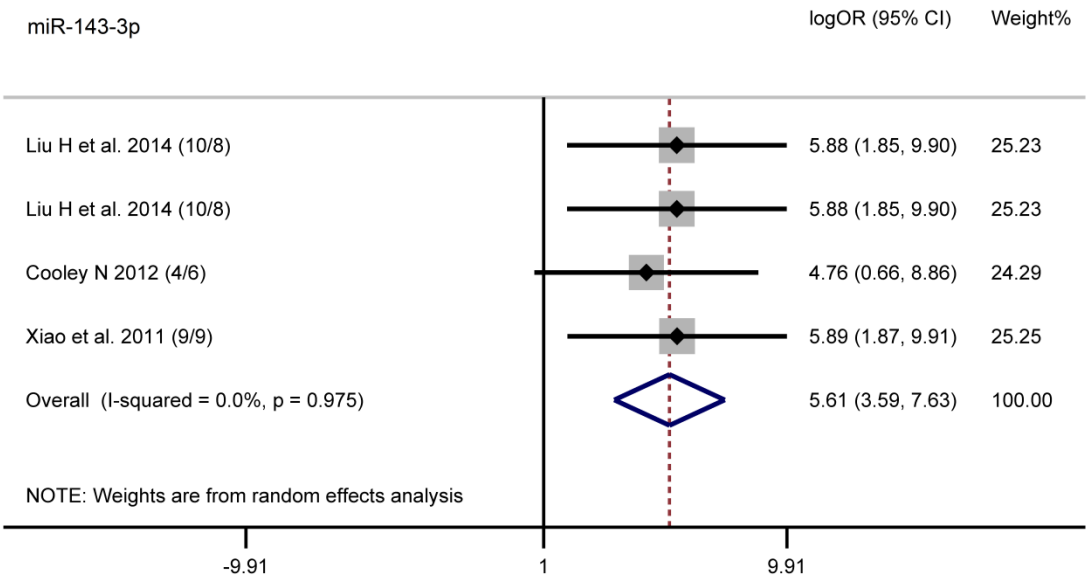
Supplementary Figure37. Forest plot of miR-133



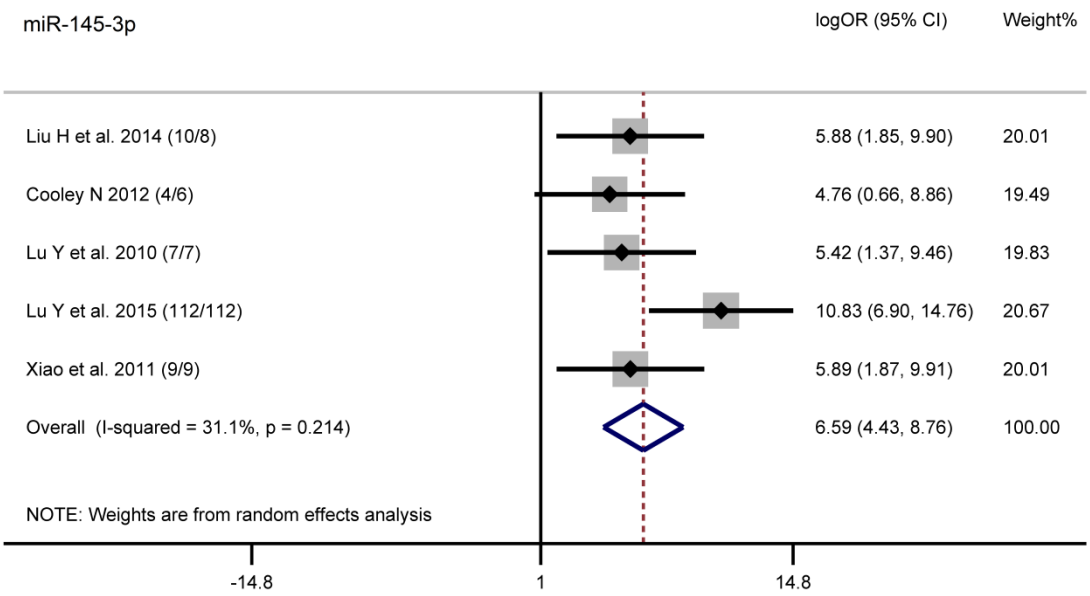
Supplementary Figure38. Forest plot of miR-133a-5p



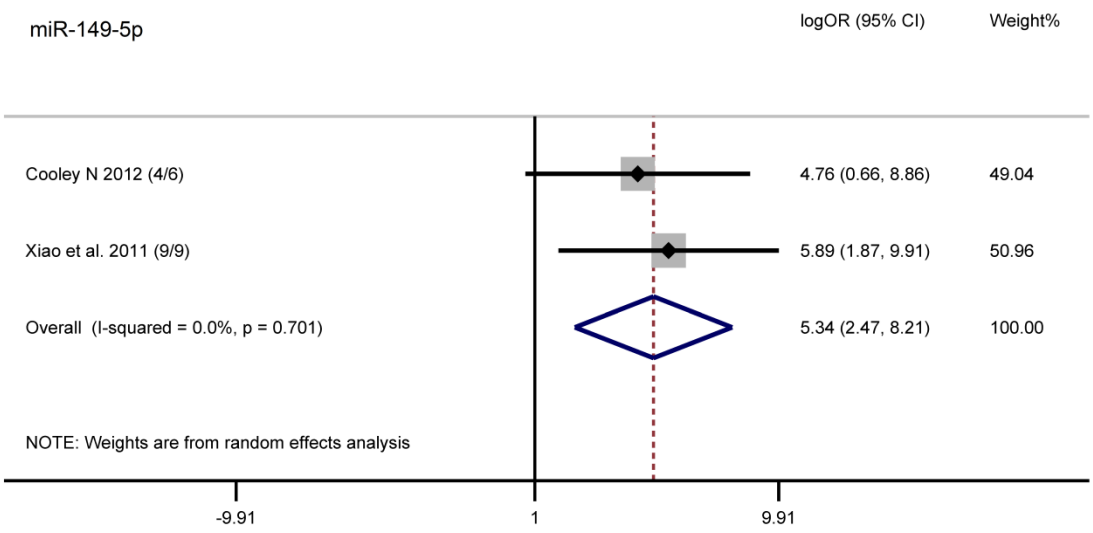
Supplementary Figure39. Forest plot of miR-139-5p



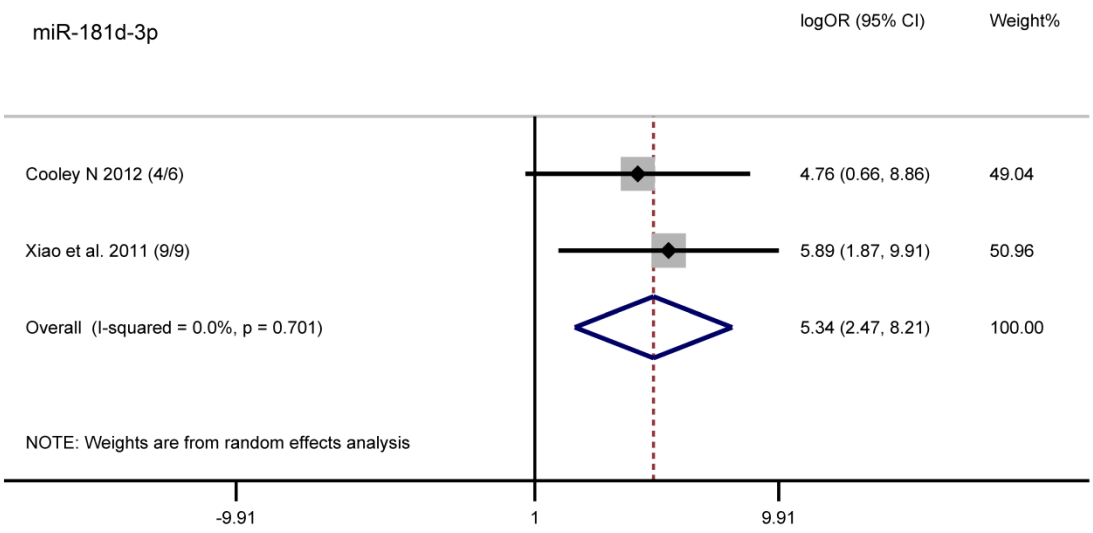
Supplementary Figure40. Forest plot of miR-143-3p



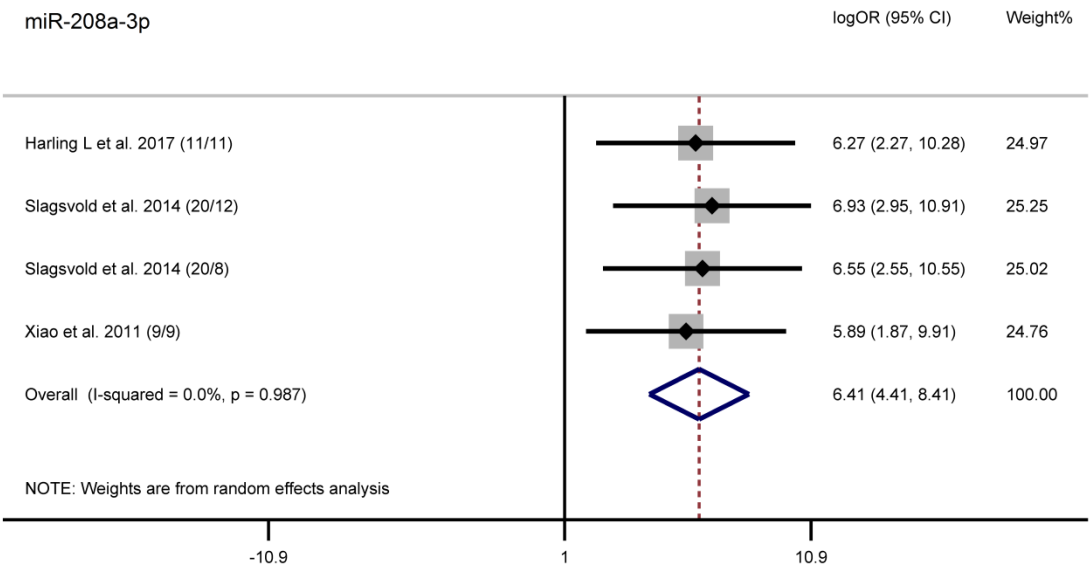
Supplementary Figure41. Forest plot of miR-145-3p



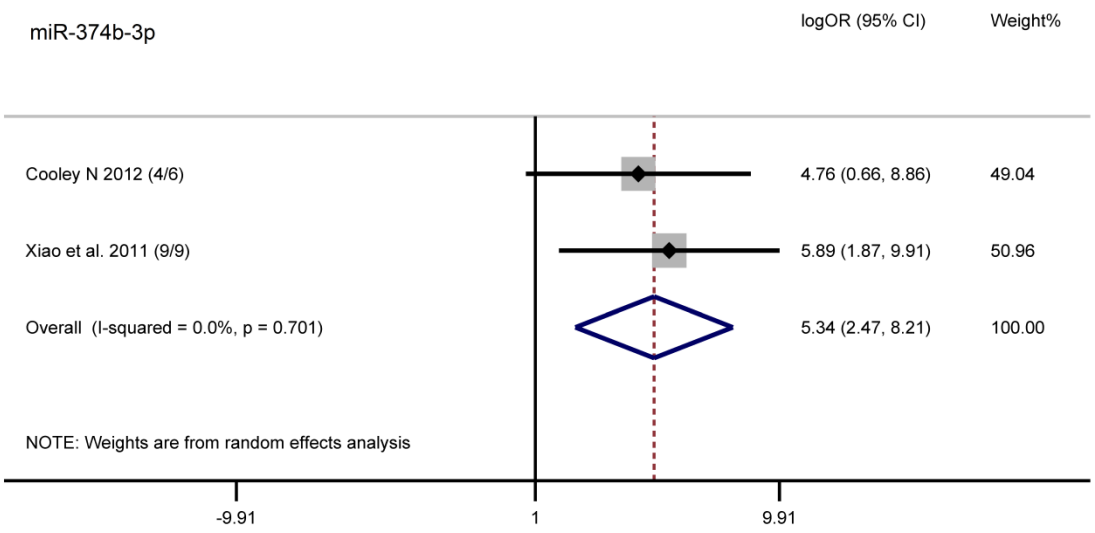
Supplementary Figure42. Forest plot of miR-149-5p



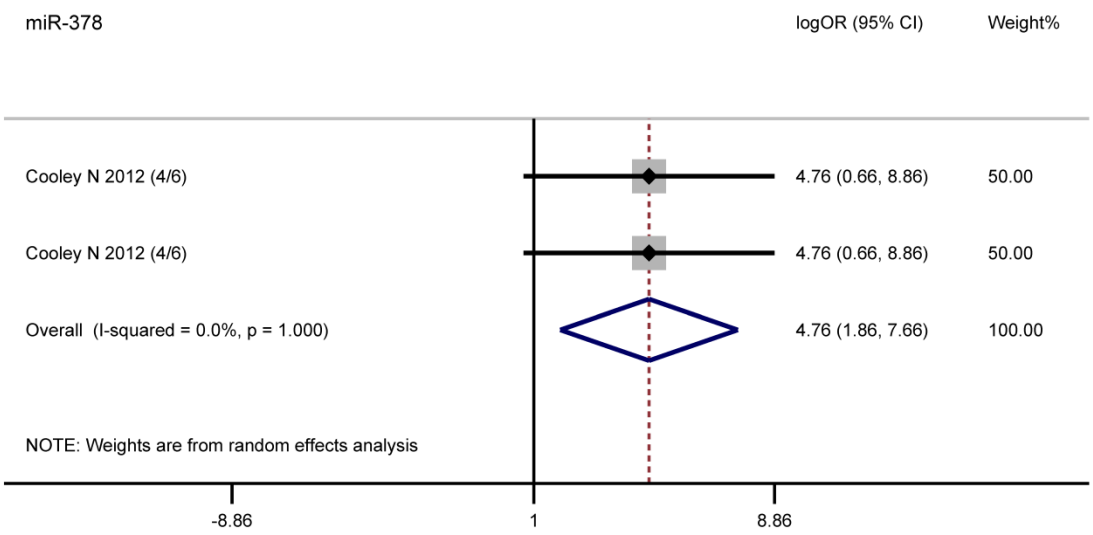
Supplementary Figure43. Forest plot of miR-181d-3p



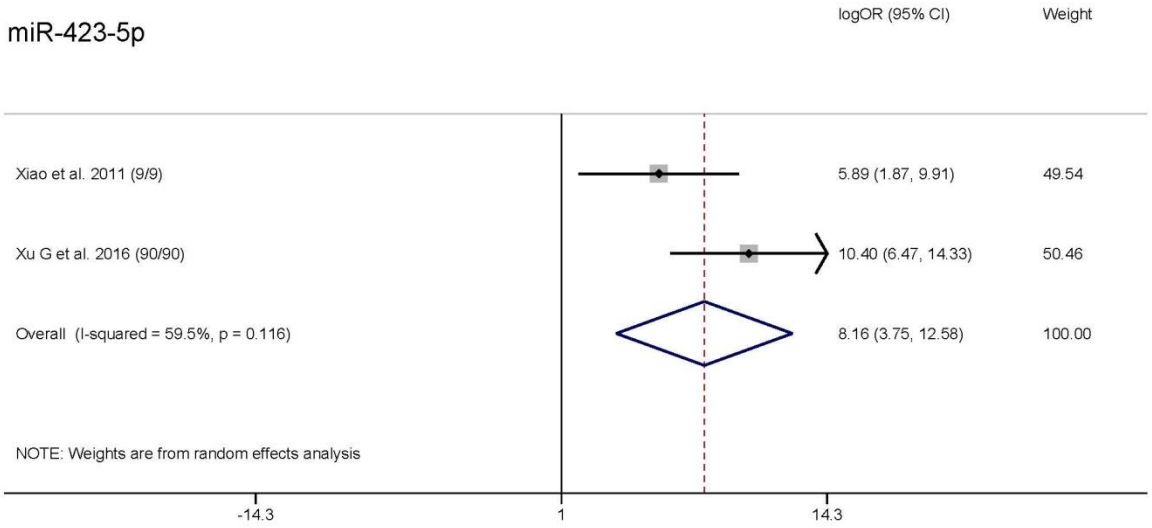
Supplementary Figure44. Forest plot of miR-208a-3p



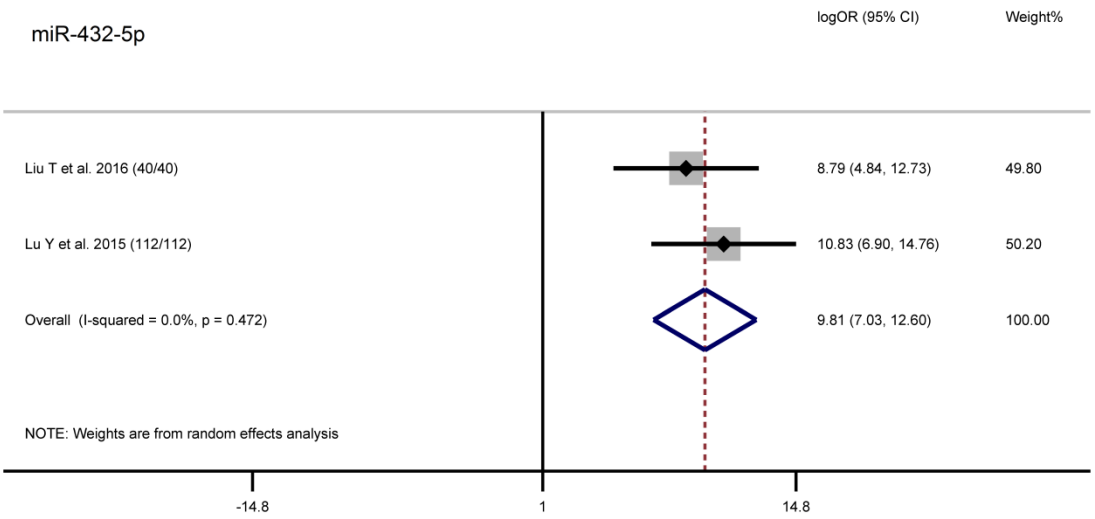
Supplementary Figure45. Forest plot of miR-374b-3p



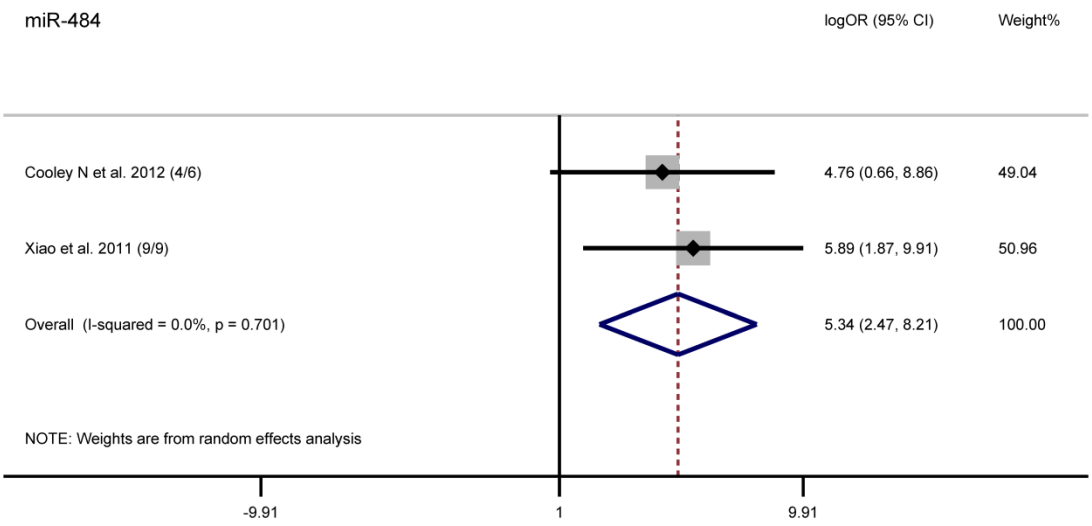
Supplementary Figure46. Forest plot of miR-378



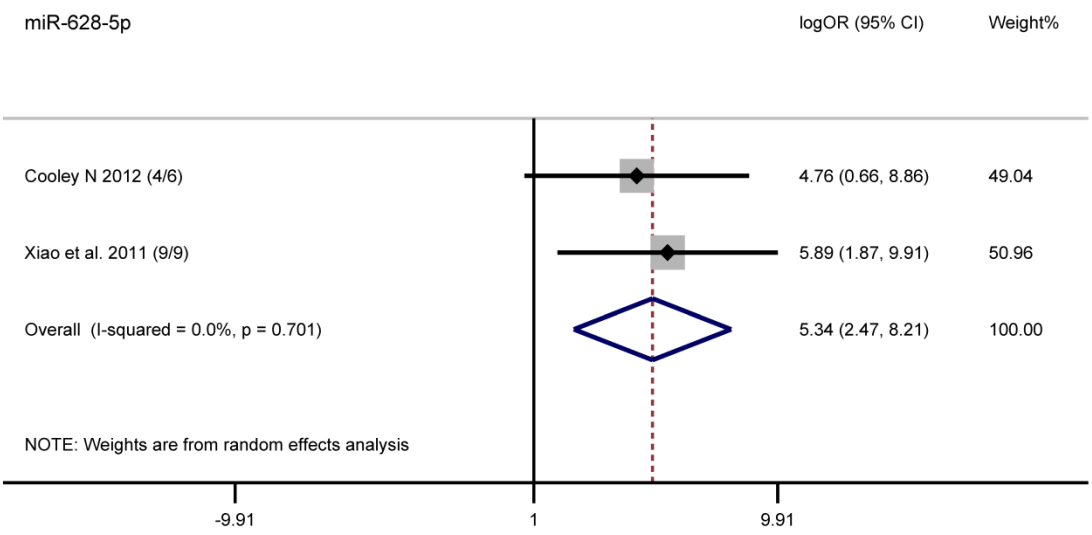
Supplementary Figure47. Forest plot of miR-423-5p



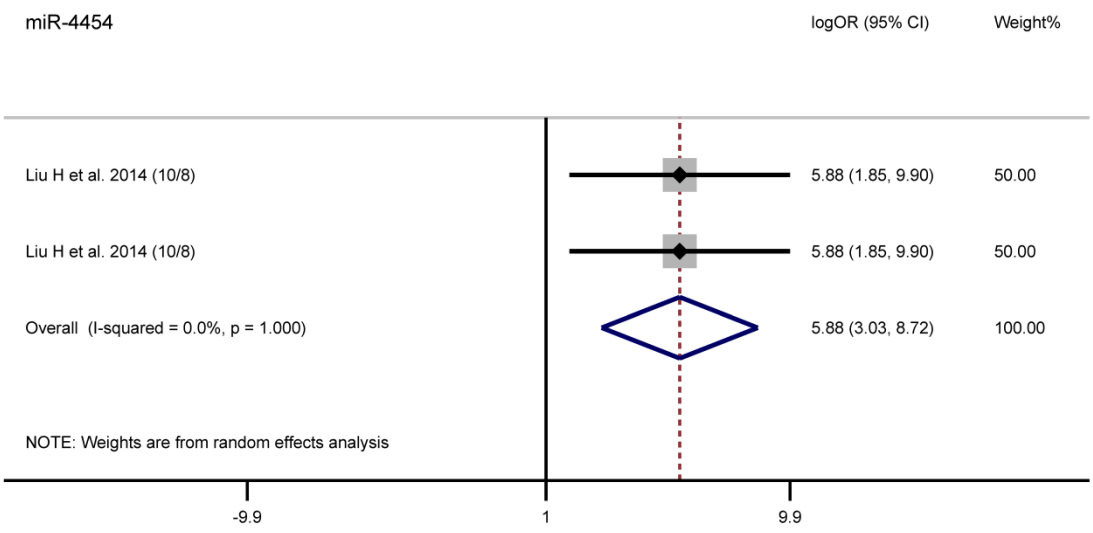
Supplementary Figure48. Forest plot of miR-432-5p



Supplementary Figure49. Forest plot of miR-484

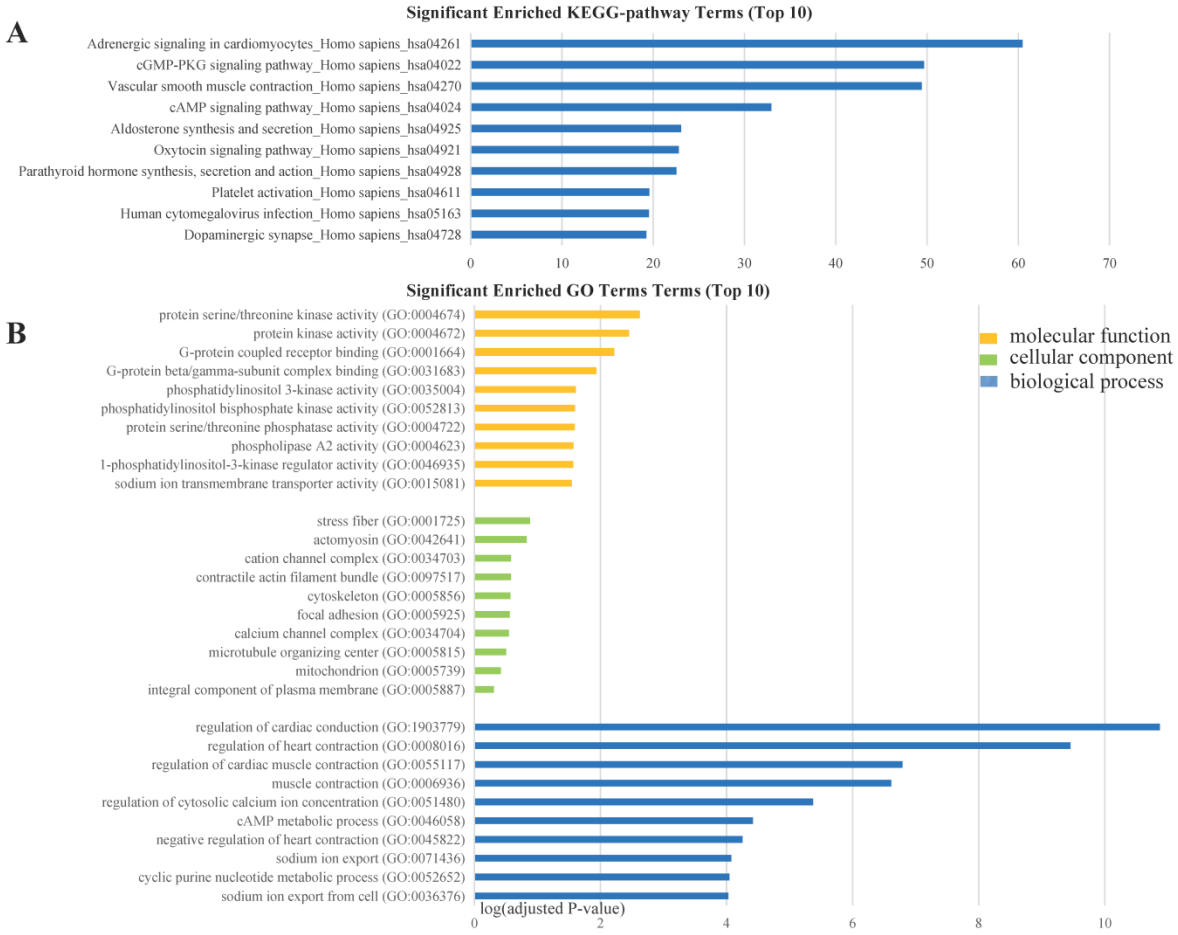


Supplementary Figure50. Forest plot of miR-628-5p



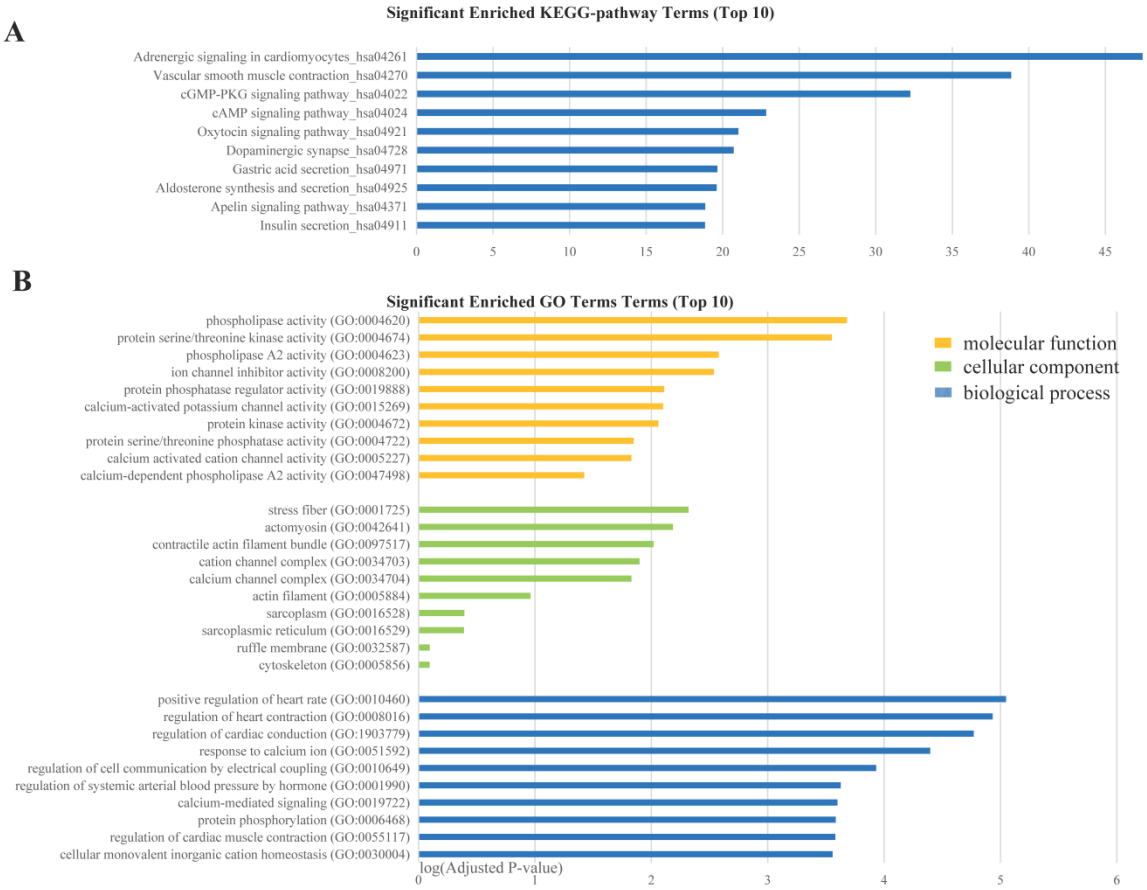
Supplementary Figure51. Forest plot of miR-4454

Supplementary Figure 52. Bioinformatic analysis for miRNAs in subgroups of sample type.



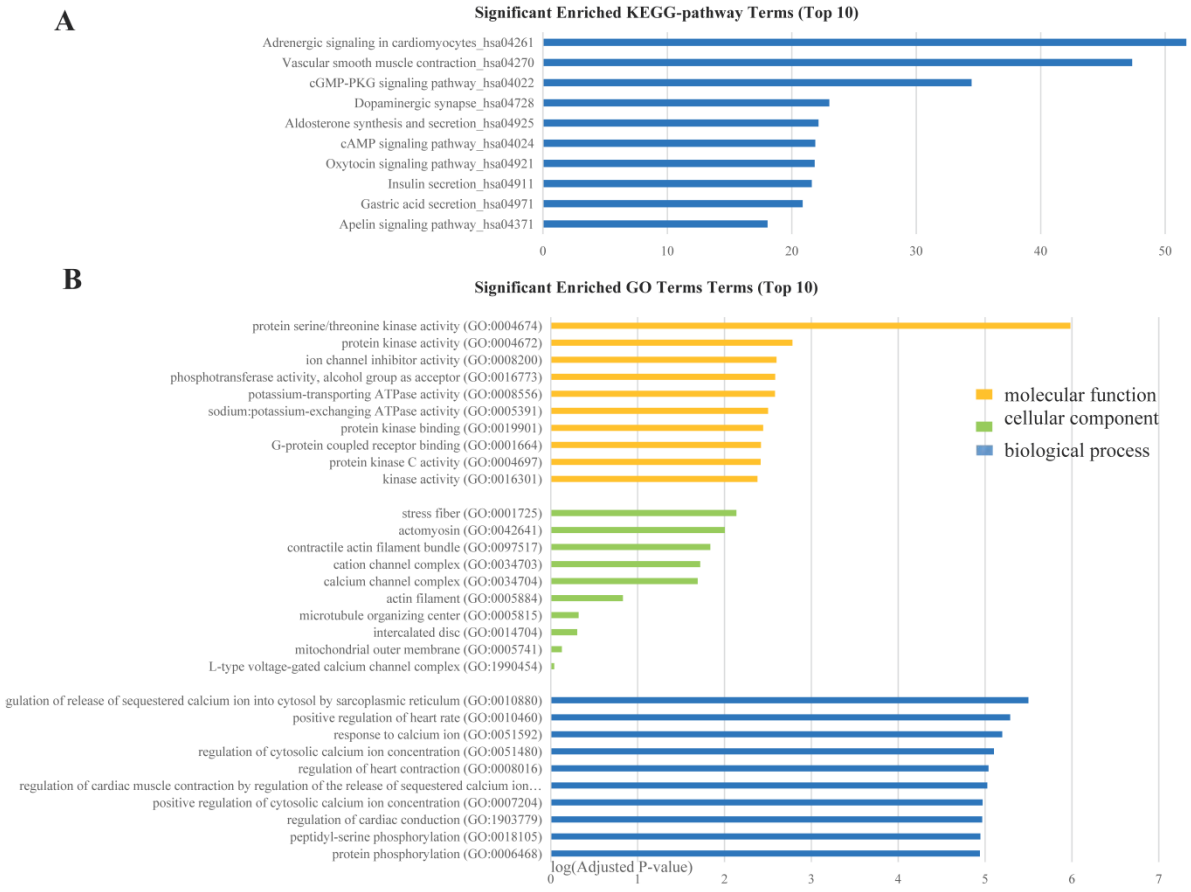
A. Top 10 terms of significant enriched KEGG pathways. B. Top 10 significant enriched GO terms, including molecular functions, cellular component and biological process.

Supplementary Figure 53. Bioinformatic analysis for miRNAs in subgroups of miRNA detecting method.



A. Top 10 terms of significant enriched KEGG pathways. B. Top 10 significant enriched GO terms, including molecular functions, cellular component and biological process.

Supplementary Figure 54. Bioinformatic analysis for miRNAs in subgroups of ethnicity.



A. Top 10 terms of significant enriched KEGG pathways. B. Top 10 significant enriched GO terms, including molecular functions, cellular component and biological process

References

1. Zhu Y, Feng Z, Cheng W, Xiao Y. MicroRNA34a mediates atrial fibrillation through regulation of AnkyrinB expression. *Molecular medicine reports* 2018;**17**:8457-65
2. Zhu H, Xue H, Jin QH, Guo J, Chen YD. Increased expression of ryanodine receptor type-2 during atrial fibrillation by miR-106-25 cluster independent mechanism. *Experimental cell research* 2018;
3. Xu GJ, Gan TY, Tang BP, Chen ZH, Ailiman M, Zhou XH, Jiang T, Song JG, Guo X, Li YD, Miao HJ, Zhang Y, Li JX. Changes in microRNAs expression are involved in age-related atrial structural remodeling and atrial fibrillation. *Chinese medical journal* 2013;**126**:1458-63
4. Wang W, Zhang K, Li X, Ma Z, Zhang Y, Yuan M, Suo Y, Liang X, Tse G, Goudis CA, Liu T. Doxycycline attenuates chronic intermittent hypoxia-induced atrial fibrosis in rats. 2018;**36**:e12321
5. Wang T, Wang B. Identification of microRNA-mRNA interactions in atrial fibrillation using microarray expression profiles and bioinformatics analysis. *Molecular medicine reports* 2016;**13**:4535-40
6. Wang M, Sun L. Ablation alleviates atrial fibrillation by regulating the signaling pathways of endothelial nitric oxide synthase/nitric oxide via miR-155-5p and miR-24-3p. 2018;
7. Wang JG, Meng X, Han J, Li Y, Luo TG, Wang J, Xin M, Xi JZ. [Differential expressions of miRNAs in patients with nonvalvular atrial fibrillation]. *Zhonghua yi xue za zhi* 2012;**92**:1816-9
8. Wang J, Song S, Xie C, Han J, Li Y, Shi J, Xin M, Wang J, Luo T, Meng X, Yang B. MicroRNA profiling in the left atrium in patients with non-valvular paroxysmal atrial fibrillation. *BMC cardiovascular disorders* 2015;**15**:97
9. Wang J, Bai Y, Li N, Ye W, Zhang M, Greene SB, Tao Y, Chen Y, Wehrens XH, Martin JF. Pitx2-microRNA pathway that delimits sinoatrial node development and inhibits predisposition to atrial fibrillation. *Proceedings of the National Academy of Sciences of the United States of America* 2014;**111**:9181-6
10. Velagaleti R, Tanriverdi K, Lin H, Esa N, Kinno M, Mandapati D, Tam S, Okike O, Ellinor P, Keaney J, Benjamin E, Freedman J, McManus D. Select cardiac microRNA are associated with prevalent atrial fibrillation and change after af ablation. *Circulation* 2014;**130**
11. Tsoporis JN, Fazio A, Rizos IK, Izhar S, Proteau G, Salpeas V, Rigopoulos A, Sakadakis E, Toumpoulis IK, Parker TG. Increased right atrial appendage apoptosis is associated with differential regulation of candidate MicroRNAs 1 and 133A in patients who developed atrial fibrillation after cardiac surgery. *Journal of molecular and cellular cardiology* 2018;**121**:25-32
12. Tsoporis J, Rizos IC, Salpeas V, Toumpoulis IK, Izhar S, Parker TG. Differential regulation of candidate micrornas 1, 133a and 328 in patients with atrial fibrillation undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass. *Canadian Journal of Cardiology* 2013;**29**:S142-S43
13. Torrado M, Franco D, Lozano-Velasco E, Hernandez-Torres F, Calvino R, Aldama G, Centeno A, Castro-Beiras A, Mikhailov A. A MicroRNA-Transcription Factor Blueprint for Early Atrial Arrhythmogenic Remodeling. *BioMed research international* 2015;**2015**:263151
14. Rizos IK, Tsoporis J, Toumpoulis IK, Salpeas V, Izhar S, Sakadakis E, Fazio A, Anastasiou-Nana M, Parker TG. Differential atrial regulation of candidate mir-1, mir-133a and mir-328 in patients following on-pump coronary artery bypass grafting. *Circulation* 2013;**128**
15. Reilly S, Liu X, Carnicer R, Rajakumar T, Sayeed R, Krasopoulos G, Verheule S, Fulga T, Schotten U, Casadei B. Evaluation of the role of miR-31-dependent reduction in dystrophin and nNOS on atrial-fibrillation-induced electrical remodelling in man. *Lancet (London, England)* 2015;**385 Suppl 1**:S82
16. Pidikiti R, Esa N, Kinno M, Ward JA, Freedman JE, Keaney J, Ambros V, McManus D. The propriety role of circulating micrornas in paroxysmal or persistent at rial fibrillation. *Journal of the American College of Cardiology* 2013;**61**:E311
17. Liu H, Chen GX, Liang MY, Qin H, Rong J, Yao JP, Wu ZK. Atrial fibrillation alters the microRNA expression profiles of the left atria of patients with mitral stenosis. *BMC cardiovascular disorders* 2014;**14**:10
18. Lei LC, Cui YX, Xu GY, Zhao NN, Wang RP, Yue YN, Yang SX. Effect of radiofrequency

ablation on miRNA expression in coronary sinus blood of patients with atrial fibrillation. *Medical Journal of Chinese People's Liberation Army* 2016;**41**:819-26
19. Chiang DY, Kongchan N, Beavers DL, Alsina KM, Voigt N, Neilson JR, Jakob H, Martin JF, Dobrev D, Wehrens XH, Li N. Loss of microRNA-106b-25 cluster promotes atrial fibrillation by enhancing ryanodine receptor type-2 expression and calcium release. *Circulation Arrhythmia and electrophysiology* 2014;**7**:1214-22
20. Berger W, Van Den Berg NWE, Jongejan A, Van Der Made I, Driessen AHG, Van Boven WJ, Pinto Y, De Groot JR. Differential expression of microRNAs associated with electrical remodeling in left atrial tissue of patients with paroxysmal versus persistent atrial fibrillation. *European heart journal* 2015;**36**:1075-76