Original Contribution

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Stroke and Circulating Extracellular RNAs

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Background and Purpose**—**There is increasing interest in extracellular RNAs (ex-RNAs), with numerous reports of associations between selected microRNAs (miRNAs) and a variety of cardiovascular disease phenotypes. Previous studies of ex-RNAs in relation to risk for cardiovascular disease have investigated small numbers of patients and assayed only candidate miRNAs. No human studies have investigated links between novel ex-RNAs and stroke.

Methods**—**We conducted unbiased next-generation sequencing using plasma from 40 participants of the FHS (Framingham Heart Study; Offspring Cohort Exam 8) followed by high-throughput polymerase chain reaction of 471 ex-RNAs. The reverse transcription quantitative polymerase chain reaction included 331 of the most abundant miRNAs, 43 small nucleolar RNAs, and 97 piwi-interacting RNAs in 2763 additional FHS participants and explored the relations of ex-RNAs and prevalent (n=63) and incident (n=51) stroke and coronary heart disease (prevalent=286, incident=69).

Results**—**After adjustment for multiple cardiovascular disease risk factors, 7 ex-RNAs were associated with stroke prevalence or incidence; there were no ex-RNA associated with prevalent or incident coronary heart disease. Statistically significant ex-RNA associations with stroke were specific, with no overlap between prevalent and incident events.

Conclusions**—**This is the largest study of ex-RNAs in relation to stroke using an unbiased approach in an observational cohort and the first large study to examine human small noncoding RNAs beyond miRNAs. These results demonstrate that when studied in a large observational cohort, extracellular miRNAs are associated with stroke risk. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.015140.)**

Key Words: cardiovascular diseases ■ genes ■ risk factors ■ RNAs ■ stroke

Plasma extracellular noncoding RNAs (ex-RNAs) are a class of circulating RNA molecules that directly modulate networks of gene expression in target tissues. Given the stability and accessibility of ex-RNAs in plasma and their potential epigenetic role in pathogenesis of disease, there has been intense interest in identifying specific ex-RNAs as diagnostic, functional, and prognostic biomarkers of a variety of systemic disorders, including cardiovascular disease (CVD). Studies in animal models of stroke have provided mechanisms by which key ex-RNAs, specifically microRNAs (miRNAs), involved in inflammation and fibrosis may modulate organ-level phenotypes.[1] In turn, the promise of these initial discoveries has engendered significant enthusiasm for ex-RNAs as novel biomarkers and therapeutic targets in patients with stroke.

Over the past 5 years, there has been burgeoning interest in ex-RNA translational investigation, with numerous reports of associations between selected miRNAs and a variety of CVD phenotypes, namely acute coronary syndromes, heart failure, coronary heart disease (CHD), and stroke. Although promising, most of these studies have relied on carefully selected populations with established disease and have largely assayed candidate miRNAs in relatively small study populations. Furthermore, to our knowledge, no human studies have investigated links between novel ex-RNAs known to modulate gene expression (eg, small nucleolar RNAs [snoRNAs] and piwi-interacting RNAs [piRNAs]) and stroke. Ultimately, the clinical translation of ex-RNAs as useful diagnostic biomarkers for stroke will rely on an unbiased evaluation in large populations.

To provide essential data for ex-RNA clinical translation, we investigated 2763 participants in FHS (Framingham Heart Study) and explored the relation of ex-RNAs to stroke and CHD. We used an unbiased 2-stage study design of

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next-generation RNA sequencing (RNASeq) for discovery followed by high-throughput reverse transcription quantitative polymerase chain reaction (RT-qPCR) to identify and quantify ex-RNAs and test their associations with stroke and CHD. To our knowledge, this report represents the largest population study identifying ex-RNAs associated with stroke or CHD.

Methods

Sample Population and Blood Collection

The FHS Offspring Cohort is a community-based, prospective study of CVD, with serial examinations every 4 to 8 years, with concomitant dense phenotyping of CVD and metabolic traits over multiple examinations. Subjects were diagnosed with stroke based on review of medical records, including relevant hospitalizations, and clinic-reported events by at least 2 neurologists agreeing on one of the following manifestations: definite cerebrovascular accident, atherothrombotic infarction of the brain, cerebral embolism, intracerebral hemorrhage, or subarachnoid hemorrhage. CHD was diagnosed if on review of the case, a panel of 3 investigators agreed on 1 of the following definite manifestations of CHD: myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, nonsudden death from CHD.

For the purposes of this analysis, prevalent cases of CHD or stroke were defined as any history recorded prior to the eighth visit for the Offspring Cohort (the second generation enrolled in the study), otherwise known as Exam 8, which is the date of the participants' ex-RNA assessment. Incident cases were defined as any case occurring during 5 years after the Exam 8 visit date.

Blood samples previously collected in the FHS Offspring Cohort participants at Exam 8 (March 2005 to January 2008) were analyzed. Venipuncture was performed on study participants in a supine position after an overnight fast by using standard venipuncture techniques. Blood was collected into blood collection tubes with a liquid-buffered sodium citrate additive (0.105 mol/L), centrifuged, and plasma separated and immediately frozen at −80°C (all steps within 90 minutes of collection). An aliquot of 170 μL of plasma samples were transferred to our laboratory in March 2014 and stored at −80°C. To assess for cellular contamination, during the isolation phase, we carefully inspected all samples for overt hemolysis. In addition, RT-qPCR results were examined for hemolysis issue based on delta C_q values for miR-23a-miR-451. A delta C_q<5 suggests little or no hemolysis and >7 is significant hemolysis.[2] For our samples, only 24 samples had a value between >7.0, representing <1% of all samples.

RNA Isolation, Library Preparation, and RNASeq

To obtain an unbiased screen of ex-RNAs from the Offspring Cohort, 40 total samples (21 with prevalent CVD and 19 age-/sex-matched FHS participants without CVD) were analyzed by RNASeq. Complete information for this data set and extensive and complete details of the specific methodology used, including quality controls for sample preparation and technologies, have been recently published.[3] Briefly, RNA was isolated from plasma samples using a miRCURY RNA Isolation Kit–Biofluids (Exiqon) per the manufacturer's protocol. A total of 130 μL plasma was used in each RNA isolation.

The Ion Total RNAseq Kit v2 (Life Technologies) was used for creating libraries for sequencing. Manufacturer's instructions were followed, with a few exceptions as previously described.[3] In collaboration with the Life Technologies R&D team, we used their underdevelopment Ion Adapter Mix to improve performance when using low template amounts. The Ion Chef System and Ion PI IC 200 kits were used for template preparation. The entire procedure was automated using the Ion Chef System. At the end of the template preparation, loaded PI Chips (Life Technologies) were placed on the sequencer. RNASeq was performed on the Ion Proton System with a sequencing depth of 10 million reads per sample. Sequencing reactions were performed on the Ion PI Chip Kit v2 BC and Ion Proton System (Life Technologies). Sequencing reads were at maximum 200 nucleotides.

Identification of Widely Expressed Ex-RNAs From RNASeq in FHS Participants

The Genboree Workbench (http://www.genboree.org/) developed by our collaborators at the National Institutes of Health as part of the Extracellular RNA Consortium was used for standard processing of small RNA reads from RNASeq. Small RNASeq reads were identified, aligned, and quantified for differential expression between CVD and non-CVD FHS participants using the exceRpt tool available on the Genboree Workbench, and full details of the package and processing were recently published.[3]

Each of the 40 small RNASeq samples from FHS participants was processed independently. The output of the pipeline is the expression values in terms of read counts for all annotated human miRNAs, piRNAs, snoRNAs, and transfer RNAs for each sample. The expression value for each sample was normalized to units of reads per million total mapped reads. Small ex-RNAs that had an average expression across 40 samples >1 reads per million total mapped reads were 669 human miRNAs, 144 human piRNAs, and 74 human snoRNAs.

Importantly, our RNASeq analysis of this limited sample size did not identify any plasma circulating ex-RNA significantly differentially expressed between prevalent CVD and non-CVD FHS participants after correction for multiple testing using the Benjamini and Hochberg false discovery rate. Given potential differences between RNASeq methodology and traditional PCR approaches used in most previous studies, we selected the most abundantly expressed ex-RNAs by RNASeq (331 miRNAs, 97 piRNAs, and 43 snoRNAs) for RT-qPCR analysis in the entire FHS Offspring Cohort as previously described.[3]

RT-qPCR of Human miRNAs, piRNAs, and snoRNAs in the Entire FHS Offspring 8 Cohort

Of the 2822 eligible subjects from the FHS Offspring Cohort at Exam 8 (baseline examination for this study), 59 (2%) subjects were excluded because of laboratory error (eg, inaccurate volume of plasma pipetted, N=31; poor protein precipitation performance, N=23; or potential contamination, N=5), resulting in 2763 subjects as a final study cohort. After removing poorly performing ex-RNA PCR assays (defined as consistent, nonvariable expression in samples, as well as no template reverse transcription control; N=15), we assayed expression of 331 human miRNAs, 97 human piRNAs, and 43 human snoRNAs. RNA was isolated using methods described earlier. RNAs were reverse transcribed as previously described[3] using a Dynamic Array 96.96 GE (Fluidigm Corp). PCR reactions were stopped at 23 cycles (C_q≤23) based on manufacturer's recommendation. It should be noted that because of the decreased volume using the Dynamic Array, this C_q is equivalent to a C_q of ≈30 by standard larger volume PCR methods with similar to superior reproducibility.

Statistical Analysis

As described earlier, we studied plasma samples from 2763 subjects. All statistical analyses were performed using STATA 13.0. Descriptive statistics are displayed as mean±SD for continuous variables and count (percentage) for categorical variables.

Model Fitting

Only those ex-RNA expressed in at least 100 FHS participants were included in RT-qPCR analyses (301 miRNAs, 59 piRNAs, and 38 snoRNAs; see Tables I and II in the online-only Data Supplement for lists of included and excluded ex-RNA). Ex-RNAs were considered expressed when C_q values were <23 (the upper limit for PCR reactions using the Biomark platform). Logistic regression models were used to identify ex-RNAs associated with prevalent CVD phenotypes, and Cox-proportional hazards models were used to identify ex-RNAs associated with incident cases occurring within 5 years of follow-up. The 5-year all-cause mortality rate in these data is 9.9 (8.6–11.5). Any impact of competing risk would likely be small because all cases of death and CVD onset are highly reviewed by the FHS, and biased results because of censoring would require very strong associations between mortality and also be strongly linked with CVD.

For both sets of analyses, multivariable regression models were fitted adjusting for known and suspected CVD risk factors (all assessed at the same examination and in fasting subjects). In addition to age and sex, these factors included smoking status (≥1 cigarette per day during the year prior to examination), systolic blood pressure, diastolic blood pressure, total cholesterol to high-density lipoprotein ratio, triglycerides, glucose level, diabetes mellitus (fasting plasma glucose ≥126 mg/dL or treatment with blood glucose–lowering medication[4]), hemoglobin A1C, C-reactive protein, lipid-lowering therapy, antihypertensive therapy, and regular aspirin use (at least 3× per week).

Hypothesis Testing

Bootstrapping was used to estimate unbiased test of statistical significance using resampling with replacement (N=50) for each of the multivariable regression models fitting CHD or stroke as a function of ex-RNA indicators of expression and confounding risk factors. To account for the number of statistical comparisons conducted for each of the 398 ex-RNAs assessed for the prevalence and incidence of stroke or CVD, we used false discovery rate correction within phenotype for logistic regression and Cox-proportional hazards models.

Results

Characteristics of the 2763 FHS participants included in our validation analysis are shown in Table 1. Of the eligible individuals, 286 (10%) had prevalent CHD and 63 (2%) had prevalent stroke. The average duration from event diagnosis to the date of the baseline examination was 12.8±9.1 years for CHD events and 8.3±7.9 years for stroke events. A total of 69 (3%) at-risk participants developed an incident CHD event and 51 (2%) developed an incident stroke within 5 years of the baseline visit. The mean follow-up time to event was 2.2±1.3 years for CHD events and 2.5±1.6 years for stroke events.

Table 1. Clinical and Demographic Characteristics of FHS Cohort (Offspring 8)

	Total N=2763 (Mean±SD/N (%))
Coronary heart disease (CHD)	
Prevalent	286 (10%)
Incident	69 (3%)
Stroke	
Prevalent	63 (2%)
Incident	51 (2%)
Age, y	66.3±8.9
Sex (female)	1499 (54%)
SBP	128.5±17.2
DBP	73.5±10.1
Triglycerides	118.4±75.6
Total:HDL cholesterol	3.5±1.1
C-reactive protein	3.3±7.4
Diabetes mellitus	431 (16%)
Glucose	106.7±23.8
A1C	5.7±0.7
Current smoker	247 (9%)
Aspirin 3/week	1216 (44%)
Antihypertensive Rx	1466 (53%)
Lipid-lowering Rx	1336 (48%)

DBP indicates diastolic blood pressure; FHS, Framingham Heart Study; HDL, high-density lipoprotein; and SBP, systolic blood pressure.

Ex-RNAs associated with prevalent and incident CHD or stroke are listed in Table 2, and the complete results for all ex-RNA modeled with multivariable regression is given in Table III in the online-only Data Supplement (full results for prevalent and incident CHD available in Table IV in the online-only Data Supplement). After adjustment for the number of ex-RNA assessed, there were no significant associations with prevalent CHD, but 3 miRNAs and 1 snoRNA were associated with prevalent stroke. We fit an additional adjusted multiple logistic regression model including all of the significant ex-RNA and found that each was independently associated with prevalent stroke: hsa-miR-877-5p (odds ratio, 0.18; 95% confidence interval [CI], 0.06–0.52; P=0.002), hsa-miR-124-3p (odds ratio, 0.29; 95% CI, 0.11–0.72; P=0.008), hsa-miR-320d (odds ratio, 0.33; 95% CI, 0.14–0.78; P=0.01), and SNO1402 (odds ratio, 0.20; 95% CI, 0.07–0.52; P=0.001). In each case, individuals with prevalent stroke at baseline were significantly less likely than those without stroke to express the ex-RNA.

There were no ex-RNA associated with incident CHD, but 3 miRNAs were associated with incident stroke (Table 2). We fit additional Cox-proportional hazards models to assess the independence of hsa-miR-656-3p, hsa-miR-3615, and hsa-miR-941 with stroke risk. Hsa-miR-3615 was no longer statistically significant after adjusting for the other significant miRNAs, but both hsa-miR-656-3p (hazard ratio [HR], 0.33; 95% CI, 0.16–0.68; P=0.003) and hsa-miR-941 (HR, 2.2; 95% CI, 1.2–4.2; P=0.013) remained significantly associated with incident stroke risk adjusting for each other and potentially confounding clinical variables.

Both hsa-miR-941 and hsa-miR-656-3p were commonly expressed with 48% (N=1306) and 49% (N=1324) of the at-risk FHS samples with a C_q<23, but the distribution of expression values differed at baseline between stroke cases and controls (Figure [A]). To assess the impact of relative expression of hsa-miR-941 and hsa-miR-656-3p, we stratified the sample into those not expressing each miRNA and among those expressing the miRNA if there was greater than or less than average expression relative to the modified global mean normalized value 18.8 (Table 3). The distribution of hsa-miR-656-3p was not even, with only 2% (N=56) of participants expressing more hsa-miR-656-3p than the global mean value. The reduced risk for stroke associated with hsa-miR-656-3p was similar in those with low and high expression, but limited sample size of those with high expression strata led to wide confidence intervals and P>0.05 (Table 3). hsa-miR-941 was more normally distributed around the global mean expression values (Figure [A]); the increased risk for stroke was similar and statistically significant for those with high and low expression (Table 3). These results suggest that it is the absolute expression of these miRNAs rather than the relative expression that best predicts stroke risk.

We stratified the sample into groups defined by the coexpression of hsa-miR-656-3p and hsa-miR-941 (Figure [B]). The greatest 5-year risk for stroke was observed in subjects expressing hsa-miR-941 but not hsa-miR-656-3p. There was no statistically significant differences in stroke risk among the

Table 2. Association With Ex-RNA Measured in Plasma at Exam 8 With the Incident and Prevalent Stroke or CHD in the FHS Cohort (Offspring 8)

	Ex-RNA	N (%)	Prevalent Cases, OR (95% CI), *P* Value	Incident Cases, HR (95% CI)
Stroke	hsa-miR-877-5p	271 (9.8)	0.10 (0.05–0.21), *P*=2.4e-09*	0.48 (0.00–5.51e+07), *P*=0.9
	hsa-miR-124-3p	279 (10.1)	0.14 (0.05–0.35), *P*=4.5e-05*	0.48 (0.00–1.75e+07), *P*=0.9
	hsa-miR-320d	231 (8.4)	0.14 (0.05–0.39), *P*=2.0e-04*	0.17 (0.00-2.94e+15), *P*=0.9
	SNO1403	260 (9.4)	0.13 (0.05–0.31), *P*=4.7e-06*	1.01 (0.36–2.82), *P*=0.9
	hsa-miR-656-3p	1358 (49.1)	1.31 (0.73–2.35), *P*=0.4	0.26 (0.13–0.52), *P*=02.0e-04*
	hsa-miR-3615	1236 (44.7)	0.80 (0.41–1.55), *P*=0.5	0.36 (0.21–0.62), *P*=03.0e-04*
	hsa-miR-941	1338 (48.4)	1.17 (0.65–2.12), *P*=0.6	3.06 (1.65–5.67), *P*=04.0e-04*
CHD	hsa-miR-181a-5p	792 (28.7)	0.59 (0.45–0.79), *P*=03.0e-04	0.69 (0.36–1.31), *P*=0.3
	hsa-miR-181c-5p	634 (22.9)	0.59 (0.43–0.83), *P*=0.002	0.77 (0.42–1.42), *P*=0.4
	hsa-miR-98-3p	179 (6.5)	0.71 (0.37–1.36), *P*=0.3	2.34 (1.27–4.32), *P*=0.01
	hsa-miR-99b-5p	2,187 (79.2)	0.82 (0.62–1.08), *P*=0.2	0.51 (0.29–0.90), *P*=0.02

HR (95% CI) indicates hazard ratio and 95% confidence intervals estimated from adjusted Cox proportional hazards models containing terms for all demographic and other CVD risk factors described in Methods and listed in Table 1. Because the CVD phenotype is the dependent variable in each adjusted model, the coefficients and effect estimates for the known and suspected confounders test for association with CVD and are not a test of association with the included ex-RNA. The results from logistic regression models predicting the expression status of each significant ex-RNA as a function of the variables included for adjustment are available in Table IV in the online-only Data Supplement. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; FHS, Framingham Heart Study; HR, hazard ratio; and OR, odds ratio.

*Ex-RNA that survived correction for multiplicity (ie, maintaining a false discovery rate <5%).

remaining groups (*P*=0.3) and each—relative to those expressing only hsa-miR-941—were at reduced risk: those expressing only hsa-miR-656-3p (HR, 0.2; 95% CI, 0.07–0.4; *P*<0.001), those expressing neither (HR, 0.4; 95% CI, 0.2–0.8; *P*=0.01), and those expressing both (HR, 0.2; 95% CI, 0.07–0.7; *P*=0.01).

Discussion

The principal objective of our study was to identify and validate ex-RNA signatures of stroke from plasma in participants of the FHS. The results demonstrate that when studied in a large observational cohort, miRNAs are limited discriminators of prevalent and incident CHD but are significantly associated with stroke. The results suggest that varieties of ex-RNAs, in addition to miRNAs, may characterize stroke. Although there have been other studies using samples from known stroke biosamples, to our knowledge, this is the largest, unbiased, community-based report of association between plasma circulating ex-RNAs (miRNAs, piRNAs, and snoRNAs) and stroke.

The role of ex-RNAs in epigenetic control of gene expression networks has become an intense area of investigation. Studies in animal models of atherosclerosis have elucidated mechanistic roles for tissue expression of miRNAs in essential aspects of CVD pathogenesis, including endothelial dysfunction, inflammation, hypertrophy, fibrosis, and apoptosis. Given that ex-RNAs are released into circulation and may even

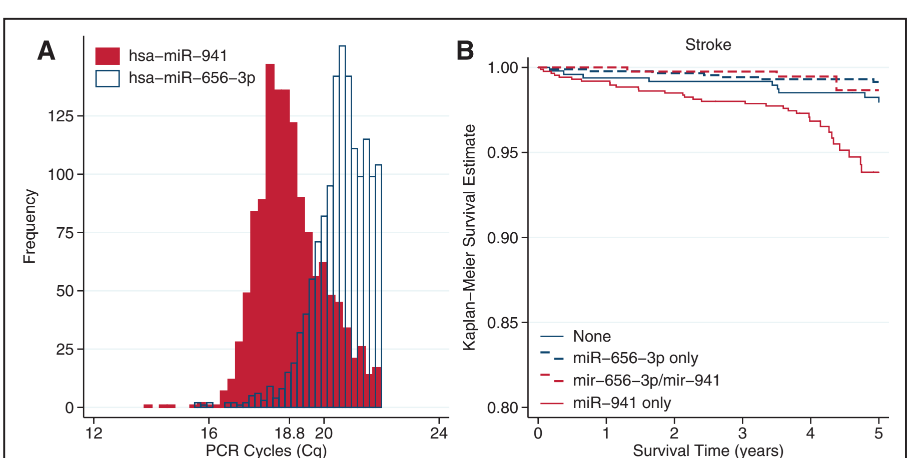

Figure. Novel ex-RNA associations with prevalent cardiovascular disease and cardiovascular risk factors in the Framingham Heart Study Offspring 8 Cohort. **A**, Represented as percent of total expressed. **B**, The survival rates observed in the 4 groups were statistically significantly different after adjustment for other risk factors (Wald's $X^2_{df=3}$=22.7; *P*<0.001). PCR indicates polymerase chain reaction.

Table 3. Impact of Relative Expression Level of hsa-miR-656-3p and hsa-miR-941 on Association With Stroke Incidence

Ex-RNA	N (%)	C_q, Mean±SD	Incident Stroke, HR (95% CI)
hsa-miR-656-3p			
None	1376 (51)	…	Ref
Low expression	1268 (47)	20.7±0.8	0.24 (0.11–0.51), $P<0.001$
High expression	56 (2)	18.3±0.9	0.54 (0.07–3.95), $P=0.5$
hsa-miR-941			
None	1394 (52)	…	Ref
Low expression	567 (21)	19.9±0.9	3.15 (1.53–6.48), $P=0.002$
High expression	739 (27)	18.1±0.6	2.99 (1.50–5.94), $P=0.002$

mi-RNAs were considered to have low (high) expression if C_q was greater (lesser) than global mean expression value of 18.8. HR (95% CI) indicates hazard ratio and 95% confidence intervals estimated from adjusted Cox-proportional hazards models containing terms for CVD risk factors described in Methods and listed in Table 1. CI indicates confidence interval; CVD, cardiovascular disease; and HR, hazard ratio.

function as molecular mediators at a distance, there has been a growing body of literature attempting to define a plasma ex-RNA signature of different CVD states. Most of the efforts in clinical translation in CVD have focused on microarray-based discovery of candidate ex-RNAs (nearly exclusively miRNAs) in well-defined disease subsets. However, most discovery efforts have been limited by small sample size and relied on careful cohort selection (eg, plasma profiles at a specific time after acute myocardial infarction) to minimize confounding.

In response, studies have been undertaken to clarify the diagnostic and prognostic ability of miRNA in CVD. In general, most measure associations between selected candidate miRNAs and CVD outcome or diagnosis, despite the well-established associations among miRNAs,[5] promiscuous mRNA targets and complex regulation,[6] and consequent biological functions within networks. Few have examined the association of ex-RNAs with stroke. Finally, whether the discriminatory ability of ex-RNAs (including those other than miRNAs) for stroke and CHD is generalizable to a large, undifferentiated, community-based cohort with and without chronic CVD remain undefined.

We sought to address these key limitations using a large, community-based cohort (the FHS) with an unbiased approach to discovery (RNASeq) and a broader profile of ex-RNAs, rather than single candidate miRNA associations. Although we did not identify miRNAs, piRNAs, or snoRNAs by RNASeq that were differentially expressed between patients with and without CVD, likely because of the size of the exploratory cohort, the significant expansion to the full cohort demonstrated significant associations with stroke.

When specifically considering CHD and miRNAs, our findings were not consistent with many previous studies that show significant associations. Reasons for this include lack of consistent miRNA detection in the literature, the use of limited candidate approaches for picking miRNAs, differences in methodology, and size of previous studies. Consistent with our modest miRNA–CHD associations, the use of miRNAs to predict short-term prognosis has been generally inferior to cardiac troponin[7,8]—perhaps owing to strong associations between miRNAs and troponin.[9,10]

Preclinical studies have demonstrated the differential expression of miRNAs in brain and blood after ischemic or hemorrhagic cerebral damage,[11] and specific small RNAs, miRNAs-19b, -29b-2*, and -339-5p, show an early and sustained upregulation in ischemic models of stroke.[1] Downregulation of miR-181b in mouse brain after ischemic stroke induces neuroprotection against ischemic injury through targeting heat shock protein A5 and ubiquitin carboxyl-terminal hydrolase isozyme L1.[12] It has been shown that target mRNA expression is correlated with the regulation of miRNA.[13] Bioinformatics show that DNA methyltransferase 3a is a major target of miR-29c. It has been suggested that miR-29c is a prosurvival miRNA, and its downregulation is a promoter of ischemic brain damage by acting through its target.[14] Additionally, intracerebral hemorrhage alters both the abundance and the compartmentalization of several inflammation-related miRNAs in plasma.[15] Importantly, treatment to reverse these effects has yet to be clearly established. Data have shown that there is no consistent change in any of the miRNAs tested between resveratrol and vehicle groups, indicating that miRNAs play a minimal role in resveratrol-mediated cerebral ischemic tolerance.[16] One proposed mechanism for small RNA modulation of stroke is that miRNA-107 may contribute to poststroke angiogenesis by targeting Dicer-1.[17] Finally, although we did not find an association for any of the piRNAs measured, it has been shown that many piRNAs are expressed in adult rodent brain, and several of them respond to focal ischemia.[18]

There have been smaller but highly informative clinical studies showing association between clinical stroke and miRNA expression. In 48 patients, several miRNA were differentially expressed in blood cells of patients with acute ischemic stroke.[19] Another study of 197 patients showed that circulating miR-30a, miR-126, and let-7b were associated with ischemic stroke.[20] In a study of 136 patients, elevated miR-106b-5P and miR-4306 and decreased miR-320e and, consistent with our findings, miR-320d in plasma were associated with acute stroke.[21] Notably, no previous studies in stroke examined piRNAs or snoRNAs.

In our findings, incident stroke was significantly associated with miR-941. miR-941 was a commonly expressed ex-RNA (48%), and we found that both those with high and low expression were at increased risk of stroke over 5 years. This specific observation is of particular interest because we have found miR-941 to be highly heritable.[22] Importantly, in a study that explored in human evolution,[23] miR-941 emerged de novo in the human lineage and is highly expressed in brain, affecting genes involved in neurotransmitter signaling.

Our data show that 3 miRNAs (miR-877-5p, miR-124-3p, and miR-320d) were associated with prevalent stroke. miR-124-3p is highly expressed in the developing and adult vertebrate brain and is involved in a broad spectrum of biological functions in the central nervous system.[24] Recently, miR-124-3p was associated with stroke and damage caused by ischemic injury in the acute setting.[24] It has been shown to regulate cell proliferation in the setting of astrocytoma.[25] miR-320d has been investigated in various cancers, and its expression has been shown to suppress cell growth, migration, and invasion and alter levels of MMP-2, MMP-9, N-cadherin, and Integrin-β1.[26] Although abundant in the cerebellum, there has been no clear pathway target for miR-877-5p.

Our study also included novel ex-RNAs (piRNAs and snoRNAs) with potent modulatory capacity on gene expression that, to our knowledge, have not been reported in large cohorts with and without stroke and CHD, representing a completely open horizon for ex-RNA biomarker discovery. Although few of these novel ex-RNAs were found to be associated with stroke, these data highlight the importance of expanding transcriptomic studies as our knowledge of these other small RNA species expands. Although we found 1 snoRNA associated with prevalent stroke (SNO1402), the mechanistic implication of this finding is unclear at this time. Specifically, the role of snoRNAs in the circulation is currently not known. SnoRNAs are a class of small RNAs that primarily guide chemical modifications of other RNAs but may function, at times, like miRNAs.

Summary/Conclusions

The strength of our study lies in (1) the use of a large, well-phenotyped cohort of individuals with and without established CVD; (2) unbiased approaches to ex-RNA discovery (RNASeq) and validated methods for high-throughput PCR-based biomarker screening; and (3) inclusion of novel ex-RNAs (piRNAs and snoRNAs) heretofore uninvestigated in clinical at-risk populations. In selecting the ex-RNAs for high-throughput PCR screening in the full cohort, we selected only the most commonly expressed miRNAs and, therefore, did not measure rare miRNAs (including some identified in previous studies of CHD). Although we cannot comment on ex-RNA origin in the circulation with our approach (cellular, vesicular, protein-bound, or free), the use of plasma (a standard source for biomarker discovery) ensures generalizability of our results.

In conclusion, in 2763 participants of the FHS, we found specific ex-RNAs associated with selected CVD phenotypes, primarily stroke. These results suggest promise for the use of ex-RNAs in the setting of stroke and suggest a focusing on discovery for mechanism, other related phenotypes, minority populations, and the use of broader populations of ex-RNAs.

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Disclosures

None.

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Stroke and Circulating Extracellular RNAs

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SUPPLEMENTAL MATERIAL

Supplemental Table I. exRNA expressed in ≥100 subjects

	Cq value		**Cq ≤23**	
exRNA	Mean	SD	N	%
hsa-let-7a-3p	20.52	1.08	835	30.2
hsa-let-7a-5p	19.43	1.24	2302	83.3
hsa-let-7b-3p	20.5	1.06	906	32.8
hsa-let-7b-5p	19.43	1.25	2277	82.4
hsa-let-7c-5p	20.17	1.01	1997	72.3
hsa-let-7d-3p	19.91	1.16	2131	77.1
hsa-let-7d-5p	19.52	1.23	2230	80.7
hsa-let-7e-5p	19.13	1.46	1319	47.7
hsa-let-7f-1-3p	20.87	1.19	433	15.7
hsa-let-7f-2-3p	20.64	1.20	551	19.9
hsa-let-7f-5p	20.19	1.04	1830	66.2
hsa-let-7g-5p	19.44	1.25	2194	79.4
hsa-let-7i-5p	19.49	1.34	2136	77.3
hsa-miR-1-3p	20.49	1.37	329	11.9
hsa-miR-100-5p	19.11	1.32	1350	48.9
hsa-miR-101-3p	18.76	1.27	2529	91.5
hsa-miR-103a-3p	19.59	1.16	2241	81.1
hsa-miR-106b-3p	18.08	1.81	1896	68.6
hsa-miR-106b-5p	17.68	1.24	2609	94.4
hsa-miR-107	20.59	1.79	279	10.1
hsa-miR-10a-5p	20.86	0.80	807	29.2
hsa-miR-10b-5p	20.38	1.09	1317	47.7
hsa-miR-1180-3p	19.73	0.99	1211	43.8
hsa-miR-122-3p	19.8	1.11	1069	38.7
hsa-miR-122-5p	17.9	1.52	2622	94.9
hsa-miR-1226-3p	20.51	1.16	904	32.7
hsa-miR-1228-5p	20.48	2.29	111	4.0
hsa-miR-1229-3p	20.71	1.53	447	16.2
hsa-miR-124-3p	20.67	1.38	279	10.1
hsa-miR-1246	17.97	2.11	1676	60.7
hsa-miR-1247-5p	18.07	1.55	1045	37.8
hsa-miR-125a-5p	19.38	1.14	2338	84.6
hsa-miR-125b-5p	19.75	1.11	2325	84.2
hsa-miR-126-3p	16.07	1.20	2669	96.6
hsa-miR-126-5p	16.75	1.17	2698	97.7
hsa-miR-1260a	18.41	1.33	2573	93.1
hsa-miR-1260b	20.31	0.95	1912	69.2
hsa-miR-1271-5p	19.42	1.01	1463	53.0

hsa-miR-128-3p	19.15	1.34	2407	87.1
hsa-miR-129-2-3p	20.45	1.47	272	9.8
hsa-miR-129-5p	20.23	1.60	177	6.4
hsa-miR-1301-3p	20.23	0.92	975	35.3
hsa-miR-1304-3p	19.44	4.73	218	7.9
hsa-miR-1306-5p	20.32	1.15	765	27.7
hsa-miR-1307-3p	20.75	1.15	375	13.6
hsa-miR-1307-5p	20.53	1.59	178	6.4
hsa-miR-130a-3p	19.49	1.17	2366	85.6
hsa-miR-130b-3p	18.98	1.27	1142	41.3
hsa-miR-130b-5p	20.74	0.97	520	18.8
hsa-miR-132-3p	20.8	1.05	831	30.1
hsa-miR-133a-3p	20.62	1.27	568	20.6
hsa-miR-134-5p	21.21	1.15	140	5.1
hsa-miR-136-3p	20.67	1.22	162	5.9
hsa-miR-136-5p	20.69	1.22	541	19.6
hsa-miR-139-5p	20.03	1.08	1794	64.9
hsa-miR-140-3p	19.19	1.15	2502	90.6
hsa-miR-141-3p	20.22	1.75	156	5.7
hsa-miR-142-3p	19.66	1.18	1025	37.1
hsa-miR-142-5p	18.68	1.33	2513	91.0
hsa-miR-143-3p	20.01	1.10	971	35.1
hsa-miR-144-3p	19.01	1.53	2072	75.0
hsa-miR-144-5p	20.84	1.08	915	33.1
hsa-miR-145-3p	20.84	1.11	256	9.3
hsa-miR-145-5p	19.43	1.18	2466	89.3
hsa-miR-146a-5p	18.42	1.16	2609	94.4
hsa-miR-146b-5p	20.16	1.16	1531	55.4
hsa-miR-148a-3p	18.31	1.47	2557	92.5
hsa-miR-148b-3p	18.55	1.34	2547	92.2
hsa-miR-150-5p	17.22	1.48	2638	95.5
hsa-miR-151a-3p	18.9	1.30	1179	42.7
hsa-miR-151a-5p	19.37	1.17	2452	88.7
hsa-miR-151b-	18.82	1.16	2606	94.3
hsa-miR-152-3p	20.41	1.10	892	32.3
hsa-miR-1537-3p	20.1	3.02	110	4.0
hsa-miR-154-3p	19.86	1.45	1035	37.5
hsa-miR-155-5p	20.94	1.11	503	18.2
hsa-miR-15a-5p	20.24	1.00	1845	66.8
hsa-miR-15b-3p	20.43	1.11	902	32.7
hsa-miR-15b-5p	16.95	1.16	2645	95.7
hsa-miR-16-2-3p	20.77	0.82	997	36.1
hsa-miR-16-5p	13.54	1.48	2716	98.3

hsa-miR-17-3p	20.71	1.40	343	12.4
hsa-miR-17-5p-	17.82	1.23	2610	94.5
hsa-miR-181a-2-3p	19.39	1.50	1768	64.0
hsa-miR-181a-3p	19.76	1.44	1045	37.8
hsa-miR-181a-5p	20.85	0.90	792	28.7
hsa-miR-181b-5p	20.77	0.87	1055	38.2
hsa-miR-181c-3p	20.82	1.05	936	33.9
hsa-miR-181c-5p	20.8	0.93	634	23.0
hsa-miR-181d-5p	20.63	1.49	1042	37.7
hsa-miR-182-5p	20.93	1.00	302	10.9
hsa-miR-183-5p	20.74	1.26	168	6.1
hsa-miR-185-3p	20.92	1.26	152	5.5
hsa-miR-185-5p	19.01	1.30	2448	88.6
hsa-miR-186-5p	19.39	1.13	2412	87.3
hsa-miR-18a-5p	19.88	1.07	2143	77.6
hsa-miR-190a-3p	19.48	1.44	792	28.7
hsa-miR-191-5p	15.99	1.85	2652	96.0
hsa-miR-192-5p	19.94	1.11	2043	73.9
hsa-miR-193a-5p	19.11	2.14	690	25.0
hsa-miR-193b-3p	19.73	1.59	738	26.7
hsa-miR-194-5p	18.51	1.49	2417	87.5
hsa-miR-195-5p	16.51	3.14	2584	93.5
hsa-miR-197-3p	19.93	0.95	2392	86.6
hsa-miR-199a-3p-	18.62	1.27	2561	92.7
hsa-miR-199a-5p	19.56	1.27	972	35.2
hsa-miR-199b-5p	19.89	1.27	1438	52.0
hsa-miR-19a-3p	15.75	1.32	2638	95.5
hsa-miR-19b-3p	15.08	1.29	2657	96.2
hsa-miR-200a-3p	20.62	1.73	163	5.9
hsa-miR-200b-3p	20.79	0.83	933	33.8
hsa-miR-200c-3p	20.96	0.69	405	14.7
hsa-miR-203a-3p	20.11	1.84	131	4.7
hsa-miR-204-5p	9.72	3.69	1663	60.2
hsa-miR-205-5p	20.47	1.12	1131	40.9
hsa-miR-206	20.85	1.31	399	14.4
hsa-miR-20a-5p	16.83	1.28	2633	95.3
hsa-miR-20b-5p	16.87	1.46	1209	43.8
hsa-miR-21-3p	20.45	1.66	179	6.5
hsa-miR-21-5p	15.85	1.40	2662	96.3
hsa-miR-2110	20.45	1.09	1159	42.0
hsa-miR-212-3p	20.05	1.16	1098	39.7
hsa-miR-214-3p	20.84	1.13	654	23.7
hsa-miR-215-5p	20.81	1.24	517	18.7

hsa-miR-22-3p	16.51	1.33	2629	95.2
hsa-miR-22-5p	20.41	1.06	1020	36.9
hsa-miR-221-3p	17.74	1.27	2648	95.8
hsa-miR-221-5p	17.79	1.68	781	28.3
hsa-miR-222-3p	19.13	1.15	2531	91.6
hsa-miR-223-3p	14.72	1.57	2665	96.5
hsa-miR-223-5p	20.8	1.08	738	26.7
hsa-miR-224-5p	20.66	1.11	753	27.3
hsa-miR-2355-5p	20.47	1.08	866	31.3
hsa-miR-23a-3p	15.88	1.18	2651	96.0
hsa-miR-23b-3p	19.37	1.13	2458	89.0
hsa-miR-24-2-5p	20.77	1.50	281	10.2
hsa-miR-24-3p	16.5	1.17	2646	95.8
hsa-miR-25-3p	16.94	1.35	2660	96.3
hsa-miR-26a-5p	17.28	1.30	2653	96.0
hsa-miR-26b-5p	17.4	1.32	2648	95.8
hsa-miR-27a-3p	17.46	1.63	2603	94.2
hsa-miR-27b-3p	19.17	1.32	2312	83.7
hsa-miR-28-3p	17.32	1.88	2471	89.4
hsa-miR-28-5p	19.56	1.36	2025	73.3
hsa-miR-296-5p	20.83	1.12	681	24.7
hsa-miR-29a-3p	16.85	1.21	2627	95.1
hsa-miR-29b-3p	19.61	1.16	2237	81.0
hsa-miR-29c-3p	16.86	1.20	2625	95.0
hsa-miR-29c-5p	20.11	1.28	1153	41.7
hsa-miR-301a-3p	20.65	1.10	885	32.0
hsa-miR-301b-3p	18.2	1.96	1683	60.9
hsa-miR-30a-3p	18.03	1.88	1522	55.1
hsa-miR-30a-5p	16.88	1.22	2667	96.5
hsa-miR-30b-5p	19.65	1.12	2327	84.2
hsa-miR-30c-5p	19.74	1.13	2269	82.1
hsa-miR-30d-5p	17.17	1.37	2648	95.8
hsa-miR-30e-3p	20.55	1.45	218	7.9
hsa-miR-30e-5p	17	1.16	2654	96.1
hsa-miR-31-3p	19.83	1.83	111	4.0
hsa-miR-32-5p	20.09	1.20	1544	55.9
hsa-miR-320a	18.52	1.18	2634	95.3
hsa-miR-320b	16.96	3.01	1978	71.6
hsa-miR-320c	20.88	1.13	606	21.9
hsa-miR-320d	20.66	1.13	231	8.4
hsa-miR-323a-3p	20.73	1.05	853	30.9
hsa-miR-324-3p	18.31	1.54	1337	48.4
hsa-miR-324-5p	20.25	0.85	1497	54.2

hsa-miR-326	20.43	1.22	559	20.2
hsa-miR-329-3p	20.49	0.98	1285	46.5
hsa-miR-330-3p	20.94	1.06	178	6.4
hsa-miR-331-3p	20.75	1.05	1000	36.2
hsa-miR-335-3p	20.73	1.32	160	5.8
hsa-miR-335-5p	20.72	0.97	1369	49.6
hsa-miR-337-3p	20.65	1.05	402	14.6
hsa-miR-337-5p	20.48	1.80	167	6.0
hsa-miR-338-3p	20.77	0.88	849	30.7
hsa-miR-338-5p	20.69	1.35	145	5.3
hsa-miR-339-3p	20.66	1.52	150	5.4
hsa-miR-339-5p	19.92	0.99	1131	40.9
hsa-miR-33a-3p	20.23	1.21	882	31.9
hsa-miR-340-5p	20.39	1.17	1478	53.5
hsa-miR-342-3p	17.76	1.10	2678	96.9
hsa-miR-342-5p	20.73	1.24	433	15.7
hsa-miR-345-5p	20.74	1.11	581	21.0
hsa-miR-34a-3p	20.49	1.38	762	27.6
hsa-miR-34a-5p	21.15	0.98	413	15.0
hsa-miR-34c-5p	20.49	0.97	1386	50.2
hsa-miR-361-5p	20.66	1.02	862	31.2
hsa-miR-3613-3p	18.41	1.60	1416	51.3
hsa-miR-3615	18.7	1.68	1236	44.7
hsa-miR-362-3p	20.2	1.13	1607	58.2
hsa-miR-363-3p	19.53	1.18	2040	73.8
hsa-miR-365a-3p-	20.42	1.06	1458	52.8
hsa-miR-374a-5p	19.97	1.32	876	31.7
hsa-miR-374b-5p-	20.38	1.20	1452	52.6
hsa-miR-375	20.45	0.95	960	34.7
hsa-miR-376a-3p	20.88	0.83	627	22.7
hsa-miR-376b-3p	18.25	1.13	1230	44.5
hsa-miR-376c-3p	20.38	1.04	1407	50.9
hsa-miR-377-3p	20.8	0.99	1018	36.8
hsa-miR-378a-3p	20.37	1.11	781	28.3
hsa-miR-378a-5p	20.73	1.19	510	18.5
hsa-miR-381-3p	20.15	1.12	915	33.1
hsa-miR-382-3p	19.53	1.81	1027	37.2
hsa-miR-409-3p	20.46	1.26	500	18.1
hsa-miR-409-5p	20	1.34	828	30.0
hsa-miR-411-3p	20.23	1.38	147	5.3
hsa-miR-423-3p	19.92	1.11	2136	77.3
hsa-miR-423-5p	19.3	1.24	2442	88.4
hsa-miR-424-3p	20.35	1.98	131	4.7

hsa-miR-424-5p	19.16	1.33	2163	78.3
hsa-miR-425-3p	19.4	1.54	1166	42.2
hsa-miR-425-5p	19.53	1.22	2017	73.0
hsa-miR-432-5p	20.17	1.15	1478	53.5
hsa-miR-433-3p	20.39	1.12	1791	64.8
hsa-miR-4429	20.1	1.04	1056	38.2
hsa-miR-4433a-5p	20.52	1.19	593	21.5
hsa-miR-4433b-3p	20.69	1.18	328	11.9
hsa-miR-4433b-5p	19.29	1.21	2428	87.9
hsa-miR-4446-3p	19.27	1.32	2509	90.8
hsa-miR-451a	11.94	1.89	2666	96.5
hsa-miR-452-5p	20.9	1.21	159	5.8
hsa-miR-454-3p	20.57	1.32	132	4.8
hsa-miR-4732-5p	20.64	0.94	562	20.3
hsa-miR-4770	20.5	1.05	1400	50.7
hsa-miR-483-3p	20.75	1.12	802	29.0
hsa-miR-483-5p	19.72	1.55	992	35.9
hsa-miR-484	17.87	1.22	2633	95.3
hsa-miR-485-3p	20.79	1.21	515	18.6
hsa-miR-486-3p	20.64	1.02	795	28.8
hsa-miR-486-5p	14.83	1.36	2706	97.9
hsa-miR-487b-3p	20.59	1.18	627	22.7
hsa-miR-494-3p	17.07	2.31	1880	68.0
hsa-miR-495-3p	20.22	1.22	662	24.0
hsa-miR-496	20.82	1.35	121	4.4
hsa-miR-497-5p	20.43	1.15	742	26.9
hsa-miR-500a-3p	20.92	0.96	370	13.4
hsa-miR-501-3p	20.64	1.43	108	3.9
hsa-miR-502-3p	20.73	1.26	110	4.0
hsa-miR-503-5p	20.56	1.60	251	9.1
hsa-miR-505-3p	20.58	1.12	808	29.2
hsa-miR-519b-5p-	20.86	0.95	1081	39.1
hsa-miR-532-3p	19.54	1.49	1935	70.0
hsa-miR-532-5p	19.5	1.72	1495	54.1
hsa-miR-542-3p	18.06	1.04	1161	42.0
hsa-miR-543	20.59	1.08	368	13.3
hsa-miR-545-5p	20.54	1.53	251	9.1
hsa-miR-548e-3p	15.95	2.57	1362	49.3
hsa-miR-550a-3p	19.74	1.62	430	15.6
hsa-miR-564	19.84	1.62	1207	43.7
hsa-miR-574-3p	19.54	1.33	2278	82.5
hsa-miR-576-5p	20.49	1.59	199	7.2
hsa-miR-582-3p	20.44	1.16	966	35.0

hsa-miR-582-5p	19.27	1.79	1065	38.6
hsa-miR-584-5p	20.7	1.27	474	17.2
hsa-miR-589-5p	20.47	1.07	831	30.1
hsa-miR-590-3p	20.59	1.46	270	9.8
hsa-miR-590-5p	20.3	1.22	706	25.6
hsa-miR-596	20.98	1.03	241	8.7
hsa-miR-598-3p	20.82	1.22	161	5.8
hsa-miR-613	20.95	0.94	497	18.0
hsa-miR-616-5p	17.49	1.25	1296	46.9
hsa-miR-624-5p	20.65	1.89	136	4.9
hsa-miR-625-3p	20.36	1.71	565	20.5
hsa-miR-627-5p	20.68	1.15	679	24.6
hsa-miR-628-3p	18.6	1.03	1217	44.1
hsa-miR-642a-5p	19.67	1.19	1044	37.8
hsa-miR-6511b-3p	19.92	1.17	2160	78.2
hsa-miR-652-3p	19.02	2.00	2080	75.3
hsa-miR-652-5p	21.05	1.02	309	11.2
hsa-miR-654-3p	20.9	1.15	198	7.2
hsa-miR-654-5p	20.88	1.44	205	7.4
hsa-miR-656-3p	20.58	0.95	1358	49.2
hsa-miR-659-3p	20.74	1.39	309	11.2
hsa-miR-660-5p	20.06	1.31	1125	40.7
hsa-miR-664a-3p	20.49	1.09	1133	41.0
hsa-miR-664a-5p	20.25	1.86	181	6.6
hsa-miR-664b-3p	16.37	3.56	1997	72.3
hsa-miR-6803-3p	20.61	1.35	174	6.3
hsa-miR-7-1-3p	20.43	1.61	220	8.0
hsa-miR-7-5p	20.78	1.17	214	7.8
hsa-miR-744-5p	14.11	3.64	1845	66.8
hsa-miR-766-3p	19.63	1.05	2010	72.8
hsa-miR-769-5p	20.58	0.99	1187	43.0
hsa-miR-7977	20.34	1.07	1779	64.4
hsa-miR-877-3p	20.89	1.33	151	5.5
hsa-miR-877-5p	20.88	1.09	271	9.8
hsa-miR-885-5p	19.71	1.34	1880	68.0
hsa-miR-9-3p	20.96	1.03	275	10.0
hsa-miR-92a-3p	15.33	1.20	2664	96.4
hsa-miR-92b-3p	16.89	1.68	1199	43.4
hsa-miR-93-3p	20.95	1.01	429	15.5
hsa-miR-93-5p	17.86	1.24	2612	94.5
hsa-miR-941	18.88	1.16	1338	48.4
hsa-miR-942-5p	20.84	1.30	375	13.6
hsa-miR-95-3p	20.62	1.48	135	4.9

hsa-miR-96-5p	20.56	1.40	377	13.6
hsa-miR-98-3p	20.34	1.68	179	6.5
hsa-miR-98-5p	20.65	1.12	685	24.8
hsa-miR-99a-5p	19.53	1.21	1947	70.5
hsa-miR-99b-5p	19.77	1.24	2187	79.2
PIR12151	18.32	1.07	2751	99.6
PIR1340	19.55	1.74	1634	59.1
PIR20101	19.93	1.16	2051	74.2
PIR2096	20.93	1.13	290	10.5
PIR212993	20.12	2.11	306	11.1
PIR218424	21.07	1.25	136	4.9
PIR2229	20.39	0.94	820	29.7
PIR22527	19.52	1.99	833	30.2
PIR227919	20.83	1.01	380	13.8
PIR23216	20.9	1.34	339	12.3
PIR232882	20.27	0.99	1566	56.7
PIR243353	20.58	1.09	1427	51.7
PIR248758	20.09	1.64	775	28.1
PIR251099	20.76	1.49	257	9.3
PIR265711	21.03	0.97	1138	41.2
PIR2888	16.3	1.57	2708	98.0
PIR2962	20.12	1.15	1561	56.5
PIR31112	19.69	1.45	1507	54.5
PIR32212	21.05	0.88	224	8.1
PIR32519	20.24	1.13	1276	46.2
PIR32636	20.7	1.10	342	12.4
PIR32637	20.59	1.16	304	11.0
PIR33384	20.6	0.83	1669	60.4
PIR33872	20.27	1.05	1736	62.8
PIR36598	20.92	1.19	138	5.0
PIR36667	21.1	0.77	526	19.0
PIR36772	20.15	1.34	1343	48.6
PIR37355	20.84	1.42	314	11.4
PIR38142	21.3	1.13	162	5.9
PIR40039	20.52	1.34	131	4.7
PIR40304	19.08	1.61	2143	77.6
PIR40506	20.86	1.50	272	9.8
PIR40766	21	1.20	157	5.7
PIR41574	21.28	1.16	175	6.3
PIR41647	20.41	0.98	1408	51.0
PIR43147	20.9	1.03	317	11.5
PIR43376	19.16	1.60	2124	76.9
PIR44080	20.9	2.05	113	4.1

PIR45809	20.48	1.21	465	16.8
PIR46251	21.18	0.97	109	3.9
PIR46358	21.19	0.96	123	4.5
PIR48383	19.6	1.44	2135	77.3
PIR49867	20.28	1.89	225	8.1
PIR49916	20.09	1.02	1847	66.9
PIR51124	19.78	1.35	1768	64.0
PIR51374	20.71	0.95	610	22.1
PIR52468	19.27	1.25	2510	90.8
PIR54042	16.01	1.61	2723	98.6
PIR54043	16.05	1.63	2720	98.4
PIR54782	20.78	1.05	210	7.6
PIR55662	20.65	1.17	307	11.1
PIR56396	21.09	1.06	196	7.1
PIR57322	19.91	1.12	1982	71.7
PIR57387	20.76	1.51	291	10.5
PIR57403	19.84	1.36	1703	61.6
PIR57576	20.09	1.30	1252	45.3
PIR57581	20.1	1.33	1230	44.5
PIR58593	20.96	1.05	212	7.7
PIR58596	20.34	1.10	1713	62.0
SNO1209	20.48	1.39	528	19.1
SNO1210	18.57	2.61	1823	66.0
SNO1257	20.3	1.73	202	7.3
SNO1277	18.83	1.34	2505	90.7
SNO1289	20.36	1.66	243	8.8
SNO1290	20.69	1.73	230	8.3
SNO1291	20.54	1.37	366	13.3
SNO1374	20.42	1.25	1205	43.6
SNO1382	20.55	1.62	265	9.6
SNO1384	20.91	1.25	656	23.7
SNO1387	20.43	1.13	1451	52.5
SNO1394	20.83	1.27	494	17.9
SNO1399	20.64	1.73	205	7.4
SNO1401	19.86	1.32	2010	72.8
SNO1403	20.43	1.65	260	9.4
SNO1405	20.28	1.53	526	19.0
SNO1407	20.19	1.81	311	11.3
SNO1408	18.45	1.42	2608	94.4
SNO1409	18.3	1.44	2625	95.0
SNO1413	20.55	1.34	684	24.8
SNO1414	20.23	1.30	1319	47.7
SNO1417	20.7	1.25	544	19.7

SNO1426	20.21	1.29	1328	48.1
SNO1441	19.36	1.13	2560	92.7
SNO1457	20.45	1.30	847	30.7
SNO1458	20.16	1.34	1393	50.4
SNO1460	19.39	1.46	2088	75.6
SNO1465	20.02	2.07	126	4.6
SNO1466	20.23	2.07	136	4.9
SNO1472	19.95	1.05	1385	50.1
SNO1490	20.01	2.15	110	4.0
SNO1502	20.49	1.13	957	34.6
SNO1507	20.92	1.23	513	18.6
SNO1549	20.22	1.92	162	5.9
SNO1550	20.79	1.12	697	25.2
SNO1562	20.02	2.20	108	3.9
SNO1563	20.49	1.30	534	19.3
SNO1568	20.6	1.43	395	14.3

Supplemental Table II. Mean Cq Values

exRNA	Cq value Mean	Cq value SD	Cq ≤ 23 N	Cq ≤ 23 %
hsa-miR-1185-1-3p	19.67	3.08	80	2.9
hsa-miR-1249-3p	19.53	1.80	38	1.4
hsa-miR-1251-5p	19.82	2.21	89	3.2
hsa-miR-140-5p	19.99	1.69	50	1.8
hsa-miR-18b-5p	20.55	1.35	98	3.6
hsa-miR-193a-3p	20.19	1.60	50	1.8
hsa-miR-210-3p	20.76	1.30	99	3.6
hsa-miR-216b-5p	21.02	1.76	38	1.4
hsa-miR-3158-3p	19.51	1.63	35	1.3
hsa-miR-33a-5p	20.28	1.58	58	2.1
hsa-miR-340-3p	20.41	1.53	76	2.8
hsa-miR-361-3p	20.53	1.60	86	3.1
hsa-miR-369-3p	20.14	1.70	64	2.3
hsa-miR-380-3p	19.07	1.54	31	1.1
hsa-miR-450b-5p	19.99	2.20	99	3.6
hsa-miR-454-5p	19.98	1.69	61	2.2
hsa-miR-487a-3p	20.51	1.47	91	3.3
hsa-miR-499a-3p	19.92	1.45	39	1.4
hsa-miR-505-5p	20.54	1.49	87	3.2
hsa-miR-5193	20.36	1.63	73	2.6
hsa-miR-520c-3p-	19.46	1.67	37	1.3
hsa-miR-545-3p	19.75	1.68	39	1.4
hsa-miR-548d-3p	19.94	1.80	54	2.0
hsa-miR-551b-3p	19.62	2.13	45	1.6
hsa-miR-552-3p	20.42	1.35	87	3.2
hsa-miR-558	20.45	1.51	90	3.3
hsa-miR-579-3p	20.53	1.48	88	3.2
hsa-miR-625-5p	16.84	4.96	41	1.5
hsa-miR-629-5p	20.26	1.50	71	2.6
hsa-miR-651-5p	20.57	1.50	83	3.0
PIR229419	20.57	2.55	24	0.9
PIR232700	20.57	2.36	15	0.5
PIR252570	18.19	5.94	10	0.4
PIR255324	20.66	2.48	71	2.6
PIR266023	18.47	6.33	52	1.9
PIR32263	19.67	3.53	10	0.4
PIR33016	20.25	2.05	41	1.5
PIR33556	20.62	2.22	26	0.9
PIR34157	14.62	4.86	4	0.1
PIR36090	19.93	2.94	20	0.7

PIR37665	21.03	1.52	89	3.2
PIR37666	20.79	1.42	84	3.0
PIR38074	19.94	3.10	11	0.4
PIR39364	13.32	2.02	3	0.1
PIR41418	19.97	2.91	16	0.6
PIR44533	21.11	1.35	41	1.5
PIR45272	20.66	2.31	15	0.5
PIR45741	20.89	1.74	52	1.9
PIR46511	21.19	1.09	66	2.4
PIR46607	20.68	1.68	41	1.5
PIR48102	20.64	2.66	12	0.4
PIR48568	20.81	1.32	73	2.6
PIR49606	15.43	5.00	3	0.1
PIR50643	20.84	1.66	56	2.0
PIR52197	20.86	1.73	55	2.0
PIR52755	20.84	2.07	31	1.1
PIR53475	19.8	3.09	11	0.4
PIR54063	21.19	1.53	73	2.6
PIR54157	19.65	3.79	7	0.3
PIR54617	20.78	2.03	37	1.3
PIR54763	15.9	5.03	3	0.1
PIR55262	19.76	1.24	3	0.1
PIR55478	19.2	3.28	7	0.3
PIR55909	16.63	6.87	8	0.3
PIR56419	20.08	1.24	71	2.6
PIR57726	20.52	1.42	76	2.8
PIR57849	21.12	0.79	63	2.3
PIR58147	19.16	3.72	10	0.4
SNO1212	19.97	2.27	93	3.4
SNO1283	19.51	2.31	84	3.0
SNO1425	19.71	1.95	72	2.6
SNO1467	19.41	2.28	74	2.7
SNO1532	18.96	2.35	56	2.0

Supplemental Table III Results for all exRNA modeled with multivariable regression

	Stroke				Coronary Heart Disease			
	Prevalent Cases		Incident Cases		Prevalent Cases		Incident Cases	
exRNA	OR (95%CI)	ɔ-valuɩ	HR (95%CI)	ɔ-value	OR (95%CI)	p-valuɩ	HR (95%CI)	p-value
hsa-let-7a-3p	0.58 (0.30, 1.14)	0.1	0.41 (0.17, 1.00)	0.05	0.93 (0.68, 1.25)	0.6	.23 (0.79, 1.92)	0.4
hsa-let-7a-5p	0.80 (0.46, 1.39)	0.4	0.47 (0.25, 0.88)	0.02	0.96 (0.65, 1.42)	0.8	.83 (0.41, 1.69)	0.6
hsa-let-7b-3p	0.97 (0.49, 1.91)	0.9	1.37 (0.76, 2.49)	0.3	1.22 (0.88, 1.68)	0.2	.60 (0.33, 1.07)	0.1
hsa-let-7b-5p	0.77 (0.37, 1.60)	0.5	0.64 (0.32, 1.26)	0.2	1.05 (0.66, 1.67)	0.8	.90 (0.44, 1.86)	0.8
hsa-let-7c-5p	1.44 (0.80, 2.59)	0.2	0.92 (0.43, 1.97)	0.8	1.16 (0.87, 1.54)	0.3	.11 (0.58, 2.13)	0.8
hsa-let-7d-3p	1.12 (0.55, 2.28)	0.8	0.96 (0.47, 1.96)	0.9	0.84 (0.61, 1.15)	0.3	.81 (0.49, 1.34)	0.4
hsa-let-7d-5p	0.98 (0.52, 1.86)	0.9	0.53 (0.27, 1.04)	0.1	0.99 (0.70, 1.41)	0.9	.03 (0.50, 2.11)	0.9
hsa-let-7e-5p	0.72 (0.36, 1.41)	0.3	0.50 (0.27, 0.94)	0.03	1.12 (0.85, 1.46)	0.4	.29 (0.77, 2.16)	0.3
hsa-let-7f-1-3p	0.87 (0.40, 1.88)	0.7	0.36 (0.00, 1.61e+07)	0.9	0.80 (0.52, 1.24)	0.3	.35 (0.78, 2.33)	0.3
hsa-let-7f-2-3p	1.36 (0.75, 2.46)	0.3	0.38 (0.00, 7101.61)	0.8	1.07 (0.73, 1.55)	0.7	.90 (0.41, 1.95)	0.8
hsa-let-7f-5p	0.98 (0.52, 1.86)	0.9	0.66 (0.36, 1.22)	0.2	1.06 (0.78, 1.44)	0.7	.86 (0.47, 1.58)	0.6
hsa-let-7g-5p	0.69 (0.33, 1.43)	0.3	0.42 (0.25, 0.71)	0	0.77 (0.52, 1.12)	0.2	.72 (0.39, 1.35)	0.3
hsa-let-7i-5p	0.83 (0.41, 1.68)	0.6	0.58 (0.31, 1.10)	0.1	1.22 (0.81, 1.84)	0.4	.25 (0.66, 2.36)	0.5
hsa-miR-1-3p	0.49 (0.19, 1.26)	0.1	0.58 (0.00, 974804.73)	0.9	0.82 (0.49, 1.37)	0.4	.58 (0.76, 3.32)	0.2
hsa-miR-100-5p	0.81 (0.43, 1.50)	0.5	0.47 (0.26, 0.86)	0.01	0.89 (0.68, 1.17)	0.4	.08 (0.66, 1.75)	0.8
hsa-miR-101-3p	1.28 (0.41, 4.01)	0.7	1.41 (0.00, 5.97e+08)	0.9	1.03 (0.62, 1.72)	0.9	.74 (0.29, 1.90)	0.5
hsa-miR-103a-3p	1.21 (0.60, 2.42)	0.6	0.79 (0.38, 1.67)	0.5	0.95 (0.64, 1.40)	0.8	.74 (0.39, 1.40)	0.4
hsa-miR-106b-3p	1.47 (0.73, 2.99)	0.3	1.90 (0.86, 4.20)	0.1	1.01 (0.75, 1.36)	0.9	.78 (0.46, 1.32)	0.4
hsa-miR-106b-5p	0.78 (0.26, 2.34)	0.7	0.67 (0.00, 10870.84)	0.9	0.92 (0.48, 1.74)	0.8	).00, 48958.55)	0.9
hsa-miR-107	0.81 (0.29, 2.26)	0.7	0.57 (0.00, 1.97e+06)	0.9	0.74 (0.44, 1.22)	0.2	.48 (0.80, 2.73)	0.2
hsa-miR-10a-5p	1.34 (0.72, 2.49)	0.4	0.75 (0.41, 1.37)	0.4	0.85 (0.63, 1.14)	0.3	.72 (0.38, 1.37)	0.3
hsa-miR-10b-5p	1.27 (0.69, 2.35)	0.4	1.45 (0.77, 2.74)	0.3	0.95 (0.69, 1.32)	0.8	.91 (0.53, 1.58)	0.7
hsa-miR-1180-3p	0.71 (0.38, 1.33)	0.3	0.37 (0.18, 0.77)	0.01	0.99 (0.73, 1.35)	0.9	.15 (0.71, 1.87)	0.6
hsa-miR-122-3p	0.93 (0.49, 1.78)	0.8	0.36 (0.17, 0.75)	0.01	1.08 (0.80, 1.47)	0.6	.88 (0.56, 1.38)	0.6
hsa-miR-122-5p	0.59 (0.22, 1.56)	0.3	0.49 (0.14, 1.67)	0.3	0.83 (0.43, 1.62)	0.6	).00, 2.15e+08)	0.9
hsa-miR-1226-3p	0.85 (0.46, 1.56)	0.6	0.88 (0.40, 1.94)	0.8	0.90 (0.63, 1.27)	0.5	.76 (0.41, 1.40)	0.4
hsa-miR-1228-5p	0.43 (0.16, 1.17)	0.1	--	--	0.82 (0.37, 1.80)	0.6	).00, 4.30e+11)	0.9
hsa-miR-1229-3p	0.93 (0.41, 2.10)	0.9	1.58 (0.72, 3.45)	0.2	0.89 (0.60, 1.31)	0.5	.06 (0.56, 2.01)	0.9
hsa-miR-124-3p	0.14 (0.05, 0.35)	####	0.48 (0.00, 1.75e+07)	0.9	0.96 (0.55, 1.67)	0.9	.26 (0.64, 2.47)	0.5
hsa-miR-1246	0.84 (0.42, 1.65)	0.6	0.53 (0.27, 1.04)	0.1	1.03 (0.80, 1.32)	0.8	.37 (0.79, 2.38)	0.3
hsa-miR-1247-5p	0.80 (0.42, 1.53)	0.5	0.39 (0.21, 0.71)	0	0.93 (0.70, 1.24)	0.6	.31 (0.81, 2.13)	0.3
hsa-miR-125a-5p	0.98 (0.47, 2.03)	0.9	0.48 (0.25, 0.91)	0.02	1.00 (0.68, 1.48)	0.9	.86 (0.48, 1.52)	0.6
hsa-miR-125b-5p	0.80 (0.45, 1.41)	0.4	0.54 (0.25, 1.13)	0.1	0.73 (0.50, 1.07)	0.1	.93 (0.55, 1.59)	0.8
hsa-miR-126-3p	1.23 (0.32, 4.68)	0.8	0.40 (0.00, 21805.32)	0.9	1.34 (0.53, 3.39)	0.5	).00, 8.64e+09)	0.9
hsa-miR-126-5p	1.67 (0.63, 4.41)	0.3	1.19 (0.00, 6.46e+14)	0.9	1.37 (0.51, 3.65)	0.5	).00, 2.13e+15)	0.9
hsa-miR-1260a	1.20 (0.43, 3.33)	0.7	0.67 (0.21, 2.17)	0.5	1.06 (0.58, 1.94)	0.9	.82 (0.27, 2.53)	0.7
hsa-miR-1260b	0.77 (0.44, 1.34)	0.4	0.59 (0.30, 1.15)	0.1	1.01 (0.76, 1.35)	0.9	.80 (0.49, 1.31)	0.4
hsa-miR-1271-5p	1.14 (0.60, 2.16)	0.7	1.45 (0.76, 2.78)	0.3	0.94 (0.74, 1.20)	0.6	.70 (0.39, 1.24)	0.2
hsa-miR-128-3p	1.09 (0.46, 2.59)	0.8	1.87 (0.58, 5.98)	0.3	1.17 (0.66, 2.08)	0.6	.01 (0.50, 2.05)	0.9
hsa-miR-129-2-3p	0.44 (0.15, 1.33)	0.1	0.51 (0.00, 4.36e+09)	0.9	0.92 (0.53, 1.62)	0.8	.02 (0.41, 2.54)	0.9
hsa-miR-129-5p	0.51 (0.18, 1.48)	0.2	0.95 (0.00, 1.64e+06)	0.9	1.19 (0.60, 2.36)	0.6	.00, 255945.42)	0.9
hsa-miR-1301-3p	0.86 (0.47, 1.57)	0.6	0.51 (0.26, 0.97)	0.04	1.09 (0.80, 1.47)	0.6	.94 (0.61, 1.44)	0.8

hsa-miR-1304-3p	0.31 (0.11, 0.91)	0.03	0.17 (0.00, 1.59e+15)	0.9	1.01 (0.59, 1.74)	0.9	.29 (0.53, 3.13)	0.6
hsa-miR-1306-5p	0.67 (0.32, 1.41)	0.3	1.04 (0.56, 1.95)	0.9	0.95 (0.70, 1.31)	0.8	.33 (0.79, 2.25)	0.3
hsa-miR-1307-3p	0.66 (0.24, 1.80)	0.4	0.41 (0.00, 1.64e+06)	0.9	1.10 (0.65, 1.86)	0.7	.56 (0.23, 1.35)	0.2
hsa-miR-1307-5p	1.38 (0.52, 3.66)	0.5	0.30 (0.00, 1.35e+16)	0.9	0.98 (0.42, 2.31)	0.9	0.00, 27735.01)	0.9
hsa-miR-130a-3p	0.80 (0.38, 1.70)	0.6	0.82 (0.37, 1.82)	0.6	0.80 (0.51, 1.25)	0.3	.91 (0.54, 1.54)	0.7
hsa-miR-130b-3p	0.72 (0.36, 1.44)	0.4	0.49 (0.26, 0.92)	0.03	0.93 (0.69, 1.25)	0.6	.19 (0.76, 1.88)	0.4
hsa-miR-130b-5p	0.87 (0.43, 1.79)	0.7	0.51 (0.21, 1.27)	0.1	0.74 (0.51, 1.07)	0.1	.01 (0.57, 1.78)	0.9
hsa-miR-132-3p	0.88 (0.40, 1.89)	0.7	0.78 (0.36, 1.73)	0.5	0.90 (0.67, 1.22)	0.5	.98 (0.57, 1.70)	0.9
hsa-miR-133a-3p	0.90 (0.36, 2.27)	0.8	0.78 (0.38, 1.62)	0.5	0.90 (0.61, 1.32)	0.6	.10 (0.55, 2.19)	0.8
hsa-miR-134-5p	1.01 (0.28, 3.67)	0.9	0.86 (0.00, 3.07e+10)	0.9	0.37 (0.14, 0.99)	0.05	.00 (0.30, 3.32)	0.9
hsa-miR-136-3p	0.46 (0.14, 1.53)	0.2	0.78 (0.00, 17936.52)	0.9	1.10 (0.59, 2.07)	0.8	0.00, 3.41e+13)	0.9
hsa-miR-136-5p	0.88 (0.43, 1.82)	0.7	0.99 (0.41, 2.44)	0.9	0.77 (0.54, 1.11)	0.2	.59 (0.26, 1.31)	0.2
hsa-miR-139-5p	0.84 (0.44, 1.60)	0.6	0.46 (0.28, 0.78)	0	0.93 (0.70, 1.23)	0.6	.00 (0.61, 1.64)	0.9
hsa-miR-140-3p	0.87 (0.39, 1.91)	0.7	1.00 (0.00, 35905.96)	0.9	1.16 (0.67, 2.01)	0.6	.71 (0.36, 1.40)	0.3
hsa-miR-141-3p	0.73 (0.22, 2.45)	0.6	0.29 (0.00, 8.84e+15)	0.9	0.87 (0.44, 1.73)	0.7	(0.00, 8396.43)	0.9
hsa-miR-142-3p	0.86 (0.44, 1.69)	0.7	0.43 (0.21, 0.89)	0.02	0.86 (0.66, 1.13)	0.3	.24 (0.73, 2.11)	0.4
hsa-miR-142-5p	0.72 (0.32, 1.60)	0.4	1.06 (0.30, 3.76)	0.9	0.94 (0.59, 1.50)	0.8	.74 (0.30, 1.83)	0.5
hsa-miR-143-3p	0.59 (0.26, 1.32)	0.2	0.54 (0.26, 1.14)	0.1	0.87 (0.66, 1.15)	0.3	.25 (0.79, 1.97)	0.3
hsa-miR-144-3p	0.73 (0.37, 1.44)	0.4	0.89 (0.46, 1.72)	0.7	0.81 (0.59, 1.10)	0.2	.03 (0.60, 1.77)	0.9
hsa-miR-144-5p	1.31 (0.71, 2.43)	0.4	1.07 (0.51, 2.22)	0.9	0.70 (0.49, 1.01)	0.1	.03 (0.63, 1.69)	0.9
hsa-miR-145-3p	0.29 (0.09, 0.97)	0.04	--	--	1.39 (0.90, 2.15)	0.1	.65 (0.95, 2.85)	0.1
hsa-miR-145-5p	1.02 (0.38, 2.78)	0.9	1.29 (0.00, 56946.56)	0.9	1.41 (0.88, 2.28)	0.2	.84 (0.43, 1.65)	0.6
hsa-miR-146a-5p	0.76 (0.25, 2.31)	0.6	0.54 (0.18, 1.62)	0.3	1.02 (0.55, 1.89)	0.9	.89 (0.26, 3.07)	0.9
hsa-miR-146b-5p	1.46 (0.74, 2.86)	0.3	0.44 (0.24, 0.81)	0.01	1.02 (0.74, 1.40)	0.9	.96 (0.57, 1.63)	0.9
hsa-miR-148a-3p	0.84 (0.30, 2.31)	0.7	0.59 (0.24, 1.46)	0.3	1.04 (0.60, 1.82)	0.9	.05 (0.34, 3.26)	0.9
hsa-miR-148b-3p	0.99 (0.32, 3.05)	0.9	0.89 (0.00, 34778.07)	0.9	0.65 (0.39, 1.09)	0.1	.97 (0.34, 2.76)	0.9
hsa-miR-150-5p	0.73 (0.23, 2.31)	0.6	0.48 (0.00, 23019.38)	0.9	0.84 (0.43, 1.64)	0.6	0.00, 1.24e+10)	0.9
hsa-miR-151a-3p	0.84 (0.45, 1.57)	0.6	0.47 (0.25, 0.88)	0.02	0.95 (0.72, 1.26)	0.7	.29 (0.83, 1.99)	0.3
hsa-miR-151a-5p	1.22 (0.49, 3.05)	0.7	1.99 (0.00, 6.82e+07)	0.9	0.94 (0.55, 1.59)	0.8	.67 (0.35, 1.30)	0.2
hsa-miR-151b-	0.79 (0.21, 3.01)	0.7	1.31 (0.00, 5.80e+11)	0.9	1.08 (0.59, 1.98)	0.8	0.00, 3.66e+09)	0.9
hsa-miR-152-3p	0.76 (0.38, 1.55)	0.5	0.61 (0.33, 1.14)	0.1	0.91 (0.67, 1.22)	0.5	.29 (0.74, 2.25)	0.4
hsa-miR-1537-3p	0.29 (0.08, 1.01)	0.1	--	--	0.57 (0.27, 1.20)	0.1	(0.00, 9436.63)	0.9
hsa-miR-154-3p	1.28 (0.72, 2.27)	0.4	1.81 (1.11, 2.97)	0.02	1.18 (0.91, 1.53)	0.2	.94 (0.55, 1.61)	0.8
hsa-miR-155-5p	0.95 (0.36, 2.51)	0.9	0.79 (0.37, 1.69)	0.5	0.98 (0.68, 1.40)	0.9	.71 (0.30, 1.68)	0.4
hsa-miR-15a-5p	1.23 (0.64, 2.35)	0.5	0.55 (0.29, 1.04)	0.1	0.94 (0.70, 1.25)	0.7	.84 (0.55, 1.29)	0.4
hsa-miR-15b-3p	0.72 (0.36, 1.42)	0.3	0.49 (0.25, 0.95)	0.04	0.80 (0.60, 1.05)	0.1	.06 (0.65, 1.71)	0.8
hsa-miR-15b-5p	0.95 (0.30, 3.04)	0.9	0.49 (0.00, 15044.03)	0.9	0.83 (0.43, 1.60)	0.6	0.00, 8.31e+06)	0.9
hsa-miR-16-2-3p	1.40 (0.79, 2.47)	0.2	1.03 (0.57, 1.88)	0.9	0.90 (0.66, 1.24)	0.5	.64 (0.37, 1.10)	0.1
hsa-miR-16-5p	--	--	0.80 (0.00, 5.65e+14)	0.9	2.40 (0.60, 9.57)	0.2	0.00, 4.10e+14)	0.9
hsa-miR-17-3p	0.87 (0.34, 2.20)	0.8	0.44 (0.00, 9.96e+07)	0.9	0.88 (0.61, 1.27)	0.5	.45 (0.79, 2.64)	0.2
hsa-miR-17-5p-	0.75 (0.25, 2.29)	0.6	0.94 (0.00, 3.58e+08)	0.9	0.80 (0.44, 1.45)	0.5	0.00, 23501.34)	0.9
hsa-miR-181a-2-3	1.20 (0.66, 2.21)	0.5	1.25 (0.69, 2.26)	0.5	0.89 (0.66, 1.19)	0.4	.98 (0.59, 1.64)	0.9
hsa-miR-181a-3p	0.81 (0.44, 1.50)	0.5	0.47 (0.25, 0.88)	0.02	0.96 (0.70, 1.30)	#####	.74 (0.44, 1.24)	0.2
hsa-miR-181a-5p	0.85 (0.46, 1.57)	0.6	0.65 (0.28, 1.54)	0.3	0.59 (0.45, 0.79)	#####	.69 (0.36, 1.31)	0.3
hsa-miR-181b-5p	1.12 (0.65, 1.91)	0.7	0.44 (0.23, 0.86)	0.02	1.06 (0.76, 1.47)	0.7	.93 (0.63, 1.38)	0.7
hsa-miR-181c-3p	0.71 (0.33, 1.52)	0.4	0.79 (0.43, 1.45)	0.4	1.24 (0.94, 1.63)	0.1	.71 (0.40, 1.26)	0.2

hsa-miR-181c-5p	0.68 (0.33, 1.43)	0.3	0.47 (0.19, 1.14)	0.1	0.59 (0.43, 0.83)	0.002	.77 (0.42, 1.42)	0.4
hsa-miR-181d-5p	0.76 (0.36, 1.61)	0.5	1.10 (0.60, 2.00)	0.8	0.94 (0.68, 1.29)	0.7	.67 (0.39, 1.17)	0.2
hsa-miR-182-5p	1.22 (0.49, 3.04)	0.7	0.84 (0.00, 8.70e+06)	0.9	1.23 (0.78, 1.94)	0.4	0.00, 12038.24)	0.9
hsa-miR-183-5p	0.85 (0.30, 2.40)	0.8	0.66 (0.00, 1.16e+11)	0.9	1.12 (0.59, 2.12)	0.7	.10 (0.41, 2.95)	0.8
hsa-miR-185-3p	1.11 (0.41, 3.00)	0.8	--	--	1.18 (0.56, 2.51)	0.7	0.00, 1.98e+14)	0.9
hsa-miR-185-5p	0.74 (0.34, 1.61)	0.4	0.80 (0.31, 2.03)	0.6	0.90 (0.55, 1.46)	0.7	.93 (0.43, 2.01)	0.9
hsa-miR-186-5p	1.10 (0.44, 2.79)	0.8	0.67 (0.31, 1.45)	0.3	0.86 (0.56, 1.32)	0.5	.97 (0.43, 2.20)	0.9
hsa-miR-18a-5p	1.42 (0.71, 2.86)	0.3	0.78 (0.44, 1.40)	0.4	0.91 (0.65, 1.27)	0.6	.89 (0.50, 1.56)	0.7
hsa-miR-190a-3p	0.91 (0.49, 1.72)	0.8	1.04 (0.52, 2.10)	0.9	0.94 (0.69, 1.27)	0.7	.83 (0.48, 1.41)	0.5
hsa-miR-191-5p	3.07 (1.34, 7.05)	0.01	0.50 (0.00, 22157.89)	0.9	1.03 (0.52, 2.05)	0.9	0.00, 1.59e+07)	0.9
hsa-miR-192-5p	1.12 (0.60, 2.09)	0.7	0.58 (0.34, 1.00)	0.1	0.99 (0.70, 1.40)	0.9	.02 (0.60, 1.74)	0.9
hsa-miR-193a-5p	1.35 (0.72, 2.52)	0.3	0.97 (0.51, 1.85)	0.9	1.01 (0.73, 1.40)	0.9	.04 (0.56, 1.92)	0.9
hsa-miR-193b-3p	1.09 (0.54, 2.22)	0.8	0.81 (0.46, 1.45)	0.5	0.91 (0.63, 1.31)	0.6	.00 (0.55, 1.81)	0.9
hsa-miR-194-5p	1.18 (0.55, 2.51)	0.7	0.81 (0.33, 2.00)	0.7	0.68 (0.46, 1.03)	0.1	.60 (0.29, 1.24)	0.2
hsa-miR-195-5p	1.04 (0.33, 3.29)	0.9	0.73 (0.22, 2.41)	0.6	0.84 (0.45, 1.60)	0.6	0.00, 3.04e+06)	0.9
hsa-miR-197-3p	0.73 (0.33, 1.61)	0.4	0.61 (0.30, 1.23)	0.2	0.75 (0.49, 1.14)	0.2	.96 (0.41, 2.25)	0.9
hsa-miR-199a-3p-	0.83 (0.31, 2.21)	0.7	0.54 (0.00, 12330.33)	0.9	0.95 (0.56, 1.62)	0.9	0.00, 1.81e+06)	0.9
hsa-miR-199a-5p	0.79 (0.38, 1.64)	0.5	0.47 (0.24, 0.93)	0.03	0.81 (0.59, 1.12)	0.2	.18 (0.70, 1.98)	0.5
hsa-miR-199b-5p	0.89 (0.47, 1.69)	0.7	0.51 (0.27, 0.98)	0.04	0.96 (0.69, 1.33)	0.8	.11 (0.62, 1.99)	0.7
hsa-miR-19a-3p	1.11 (0.34, 3.65)	0.9	0.55 (0.00, 24046.97)	0.9	0.89 (0.47, 1.70)	0.7	0.00, 2.76e+07)	0.9
hsa-miR-19b-3p	1.37 (0.46, 4.11)	0.6	2.06 (0.00, 2.66e+15)	0.9	1.16 (0.54, 2.49)	0.7	0.00, 7.64e+06)	0.9
hsa-miR-200a-3p	0.19 (0.07, 0.52)	0	0.30 (0.00, 9.71e+15)	0.9	0.31 (0.10, 0.92)	0.03	.00, 191931.32)	0.9
hsa-miR-200b-3p	0.71 (0.40, 1.25)	0.2	0.65 (0.30, 1.43)	0.3	0.85 (0.62, 1.16)	0.3	.02 (0.56, 1.86)	0.9
hsa-miR-200c-3p	1.06 (0.38, 2.94)	0.9	0.48 (0.14, 1.63)	0.2	1.25 (0.85, 1.82)	0.3	.79 (0.35, 1.74)	0.6
hsa-miR-203a-3p	0.54 (0.14, 2.00)	0.4	1.12 (0.00, 17639.56)	0.9	0.93 (0.48, 1.79)	0.8	0.00, 6.61e+06)	0.9
hsa-miR-204-5p	1.19 (0.57, 2.48)	0.6	1.56 (0.82, 2.97)	0.2	0.95 (0.72, 1.25)	0.7	.88 (0.54, 1.42)	0.6
hsa-miR-205-5p	0.99 (0.51, 1.89)	0.9	1.48 (0.72, 3.01)	0.3	0.99 (0.73, 1.34)	0.9	.71 (0.42, 1.19)	0.2
hsa-miR-206	0.77 (0.30, 1.97)	0.6	0.79 (0.31, 2.00)	0.6	1.08 (0.69, 1.71)	0.7	.12 (0.54, 2.33)	0.8
hsa-miR-20a-5p	1.19 (0.37, 3.89)	0.8	0.45 (0.00, 8000.50)	0.9	0.90 (0.48, 1.69)	0.7	0.00, 26449.03)	0.9
hsa-miR-20b-5p	0.89 (0.46, 1.73)	0.7	0.48 (0.26, 0.91)	0.02	1.00 (0.75, 1.33)	0.9	.36 (0.85, 2.19)	0.2
hsa-miR-21-3p	0.47 (0.14, 1.57)	0.2	0.53 (0.00, 4.71e+13)	0.9	0.72 (0.35, 1.49)	0.4	.76 (0.26, 2.20)	0.6
hsa-miR-21-5p	1.32 (0.44, 4.00)	0.6	0.45 (0.00, 8257.77)	0.9	0.86 (0.44, 1.68)	0.7	0.00, 3.03e+13)	0.9
hsa-miR-2110	0.89 (0.48, 1.65)	0.7	2.12 (1.14, 3.94)	0.02	1.15 (0.85, 1.55)	0.4	.86 (0.52, 1.43)	0.6
hsa-miR-212-3p	0.89 (0.50, 1.59)	0.7	3.17 (1.62, 6.22)	0	0.86 (0.63, 1.19)	0.4	.05 (0.62, 1.80)	0.9
hsa-miR-214-3p	0.78 (0.32, 1.90)	0.6	0.77 (0.29, 2.04)	0.6	1.01 (0.67, 1.53)	0.9	.13 (0.61, 2.10)	0.7
hsa-miR-215-5p	0.73 (0.31, 1.75)	0.5	1.50 (0.83, 2.71)	0.2	1.01 (0.70, 1.47)	0.9	.78 (0.33, 1.83)	0.6
hsa-miR-22-3p	1.24 (0.37, 4.10)	0.7	0.58 (0.00, 10260.15)	0.9	0.88 (0.45, 1.70)	0.7	0.00, 15474.43)	0.9
hsa-miR-22-5p	1.25 (0.71, 2.20)	0.4	0.58 (0.28, 1.20)	0.1	0.82 (0.64, 1.05)	0.1	.94 (0.55, 1.61)	0.8
hsa-miR-221-3p	1.59 (0.45, 5.59)	0.5	1.02 (0.00, 1.56e+12)	0.9	1.65 (0.59, 4.63)	0.3	0.00, 1.71e+09)	0.9
hsa-miR-221-5p	0.84 (0.42, 1.68)	0.6	1.05 (0.53, 2.09)	0.9	1.25 (0.93, 1.67)	0.1	.70 (0.32, 1.51)	0.4
hsa-miR-222-3p	1.21 (0.42, 3.45)	0.7	0.60 (0.21, 1.69)	0.3	1.25 (0.72, 2.19)	0.4	.67 (0.34, 1.35)	0.3
hsa-miR-223-3p	0.85 (0.27, 2.75)	0.8	0.43 (0.00, 11656.87)	0.9	0.82 (0.41, 1.61)	0.6	0.00, 1.20e+13)	0.9
hsa-miR-223-5p	0.63 (0.25, 1.58)	0.3	0.58 (0.27, 1.25)	0.2	1.25 (0.89, 1.76)	0.2	.10 (0.70, 1.72)	0.7
hsa-miR-224-5p	0.93 (0.44, 1.96)	0.8	0.52 (0.22, 1.20)	0.1	1.04 (0.75, 1.45)	0.8	.91 (0.52, 1.59)	0.7
hsa-miR-2355-5p	1.10 (0.58, 2.06)	0.8	1.63 (0.93, 2.86)	0.1	0.95 (0.67, 1.35)	0.8	.09 (0.65, 1.83)	0.8
hsa-miR-23a-3p	0.93 (0.29, 2.97)	0.9	0.49 (0.00, 12000.95)	0.9	0.79 (0.40, 1.55)	0.5	0.00, 1.67e+13)	0.9

hsa-miR-23b-3p	0.69 (0.31, 1.52)	0.4	1.04 (0.29, 3.76)	0.9	1.12 (0.66, 1.92)	0.7	.09 (0.40, 2.96)	0.9
hsa-miR-24-2-5p	0.78 (0.29, 2.12)	0.6	0.83 (0.00, 237427.73)	0.9	1.12 (0.77, 1.64)	0.6	0.00, 1.07e+07)	0.9
hsa-miR-24-3p	1.02 (0.32, 3.21)	0.9	0.51 (0.00, 11840.14)	0.9	0.92 (0.47, 1.81)	0.8	0.00, 2.53e+07)	0.9
hsa-miR-25-3p	0.86 (0.33, 2.24)	0.8	0.45 (0.00, 8410.68)	0.9	1.10 (0.53, 2.28)	0.8	0.00, 1.54e+13)	0.9
hsa-miR-26a-5p	0.65 (0.21, 2.04)	0.5	0.63 (0.00, 2.06e+08)	0.9	0.92 (0.45, 1.87)	0.8	0.00, 2.33e+07)	0.9
hsa-miR-26b-5p	0.53 (0.19, 1.52)	0.2	0.69 (0.00, 1.65e+08)	0.9	1.09 (0.53, 2.25)	0.8	0.00, 1.95e+09)	0.9
hsa-miR-27a-3p	1.01 (0.33, 3.07)	0.9	0.52 (0.14, 1.88)	0.3	1.04 (0.54, 2.01)	0.9	(0.00, 7400.87)	0.9
hsa-miR-27b-3p	0.63 (0.32, 1.25)	0.2	0.56 (0.26, 1.22)	0.1	1.00 (0.70, 1.42)	0.9	.89 (0.45, 1.73)	0.7
hsa-miR-28-3p	0.71 (0.28, 1.78)	0.5	1.18 (0.35, 4.03)	0.8	1.04 (0.62, 1.76)	0.9	.98 (0.44, 2.18)	0.9
hsa-miR-28-5p	1.08 (0.60, 1.96)	0.8	1.07 (0.50, 2.29)	0.9	0.70 (0.53, 0.92)	0.01	.81 (0.45, 1.46)	0.5
hsa-miR-296-5p	0.73 (0.35, 1.54)	0.4	1.35 (0.72, 2.53)	0.3	0.81 (0.58, 1.15)	0.2	.51 (0.26, 1.02)	0.1
hsa-miR-29a-3p	0.84 (0.27, 2.60)	0.8	0.59 (0.00, 17383.82)	0.9	1.01 (0.53, 1.90)	0.9	0.00, 11806.20)	0.9
hsa-miR-29b-3p	1.30 (0.63, 2.69)	0.5	0.74 (0.37, 1.47)	0.4	0.66 (0.47, 0.94)	0.02	.93 (0.51, 1.69)	0.8
hsa-miR-29c-3p	0.93 (0.29, 2.97)	0.9	0.61 (0.00, 18289.36)	0.9	0.86 (0.46, 1.61)	0.6	0.00, 11683.39)	0.9
hsa-miR-29c-5p	0.91 (0.51, 1.64)	0.8	0.64 (0.37, 1.09)	0.1	1.01 (0.75, 1.36)	0.9	.77 (0.51, 1.17)	0.2
hsa-miR-301a-3p	1.15 (0.58, 2.31)	0.7	0.64 (0.24, 1.71)	0.4	0.62 (0.43, 0.89)	0.01	.95 (0.57, 1.60)	0.9
hsa-miR-301b-3p	1.07 (0.59, 1.93)	0.8	2.64 (1.17, 5.94)	0.02	0.89 (0.68, 1.17)	0.4	.79 (0.53, 1.19)	0.3
hsa-miR-30a-3p	0.92 (0.54, 1.55)	0.7	2.94 (1.43, 6.05)	0	1.21 (0.91, 1.62)	0.2	.65 (0.38, 1.10)	0.1
hsa-miR-30a-5p	2.55 (1.03, 6.29)	0.04	0.78 (0.00, 6.98e+11)	0.9	1.26 (0.55, 2.90)	0.6	0.00, 3.60e+09)	0.9
hsa-miR-30b-5p	0.96 (0.47, 1.95)	0.9	0.62 (0.32, 1.17)	0.1	0.96 (0.65, 1.40)	0.8	.82 (0.40, 1.67)	0.6
hsa-miR-30c-5p	0.63 (0.35, 1.15)	0.1	0.87 (0.42, 1.82)	0.7	0.75 (0.49, 1.14)	0.2	.21 (0.58, 2.51)	0.6
hsa-miR-30d-5p	3.11 (1.28, 7.57)	0.01	0.67 (0.00, 1.92e+08)	0.9	1.00 (0.50, 2.02)	0.9	0.00, 9.18e+06)	0.9
hsa-miR-30e-3p	0.36 (0.11, 1.21)	0.1	0.44 (0.00, 7.22e+07)	0.9	0.53 (0.28, 1.01)	0.1	.04 (0.50, 2.15)	0.9
hsa-miR-30e-5p	0.93 (0.29, 2.94)	0.9	0.98 (0.00, 5.45e+11)	0.9	0.96 (0.47, 1.95)	0.9	0.00, 2.64e+07)	0.9
hsa-miR-31-3p	0.83 (0.21, 3.36)	0.8	--	--	1.28 (0.50, 3.30)	0.6	0.00, 35791.46)	0.9
hsa-miR-32-5p	0.55 (0.31, 0.99)	0.04	1.19 (0.58, 2.40)	0.6	0.88 (0.63, 1.23)	0.5	.95 (0.57, 1.57)	0.8
hsa-miR-320a	1.78 (0.48, 6.66)	0.4	1.17 (0.00, 8.91e+11)	0.9	1.34 (0.73, 2.44)	0.3	0.00, 30081.07)	0.9
hsa-miR-320b	0.97 (0.57, 1.67)	0.9	0.53 (0.31, 0.91)	0.02	1.29 (0.92, 1.82)	0.1	.71 (0.42, 1.20)	0.2
hsa-miR-320c	0.99 (0.49, 2.03)	0.90	0.96 (0.44, 2.11)	0.9	0.90 (0.65, 1.25)	0.5	.78 (0.38, 1.58)	0.5
hsa-miR-320d	0.14 (0.05, 0.39)	####	0.17 (0.00, 2.94e+15)	0.9	0.66 (0.32, 1.34)	0.2	.57 (0.92, 2.68)	0.1
hsa-miR-323a-3p	1.17 (0.59, 2.31)	0.6	0.70 (0.29, 1.69)	0.4	0.68 (0.49, 0.95)	0.02	.87 (0.53, 1.43)	0.6
hsa-miR-324-3p	0.72 (0.37, 1.42)	0.3	0.71 (0.38, 1.32)	0.3	0.89 (0.66, 1.19)	0.4	.52 (0.94, 2.46)	0.1
hsa-miR-324-5p	1.16 (0.63, 2.16)	0.6	1.63 (0.82, 3.22)	0.2	1.10 (0.84, 1.45)	0.5	.74 (0.43, 1.26)	0.3
hsa-miR-326	0.71 (0.29, 1.70)	0.4	0.48 (0.18, 1.26)	0.1	0.74 (0.49, 1.12)	0.2	.16 (0.69, 1.96)	0.6
hsa-miR-329-3p	1.26 (0.78, 2.02)	0.3	1.18 (0.63, 2.22)	0.6	0.75 (0.55, 1.02)	0.1	.91 (0.51, 1.62)	0.7
hsa-miR-330-3p	0.96 (0.32, 2.86)	0.9	--	--	0.90 (0.47, 1.71)	0.7	.40 (0.65, 3.01)	0.4
hsa-miR-331-3p	0.74 (0.43, 1.28)	0.3	0.92 (0.48, 1.75)	0.8	1.01 (0.75, 1.36)	0.9	.79 (0.44, 1.39)	0.4
hsa-miR-335-3p	0.40 (0.12, 1.34)	0.1	0.26 (0.00, 1.54e+15)	0.9	1.16 (0.54, 2.51)	0.7	0.00, 37503.83)	0.9
hsa-miR-335-5p	0.76 (0.47, 1.22)	0.3	0.54 (0.26, 1.12)	0.1	0.88 (0.68, 1.13)	0.3	.17 (0.76, 1.80)	0.5
hsa-miR-337-3p	1.34 (0.53, 3.35)	0.5	0.11 (0.00, 2.85e+15)	0.9	0.69 (0.46, 1.05)	0.1	.92 (0.46, 1.86)	0.8
hsa-miR-337-5p	0.77 (0.24, 2.54)	0.7	--	--	1.18 (0.66, 2.10)	0.6	0.00, 6.31e+14)	0.9
hsa-miR-338-3p	0.97 (0.47, 1.99)	0.9	0.63 (0.30, 1.36)	0.2	0.99 (0.77, 1.28)	0.9	.92 (0.56, 1.51)	0.7
hsa-miR-338-5p	0.51 (0.12, 2.11)	0.4	0.31 (0.00, 2.82e+15)	0.9	0.87 (0.45, 1.67)	0.7	0.00, 3.60e+10)	0.9
hsa-miR-339-3p	1.04 (0.32, 3.41)	0.9	0.31 (0.00, 8.01e+15)	0.9	1.10 (0.56, 2.17)	0.8	.91 (0.32, 2.59)	0.9
hsa-miR-339-5p	0.93 (0.48, 1.80)	0.8	0.60 (0.31, 1.15)	0.1	0.99 (0.74, 1.31)	0.9	.21 (0.75, 1.97)	0.4
hsa-miR-33a-3p	0.94 (0.45, 1.96)	0.9	0.51 (0.29, 0.88)	0.01	1.00 (0.75, 1.33)	0.9	.81 (0.49, 1.35)	0.4

hsa-miR-340-5p	1.15 (0.65, 2.01)	0.6	0.76 (0.45, 1.30)	0.3	0.86 (0.64, 1.17)	0.3	).74 (0.43, 1.26)	0.3
hsa-miR-342-3p	1.19 (0.41, 3.39)	0.8	0.73 (0.00, 5.82e+11)	0.9	1.27 (0.52, 3.07)	0.6	0.00, 2.63e+07)	0.9
hsa-miR-342-5p	1.01 (0.42, 2.45)	0.9	0.73 (0.23, 2.32)	0.6	1.02 (0.67, 1.54)	0.9	).60 (0.27, 1.36)	0.2
hsa-miR-345-5p	0.57 (0.22, 1.49)	0.3	0.48 (0.00, 17721.35)	0.9	0.54 (0.35, 0.84)	0.01	).77 (0.41, 1.45)	0.4
hsa-miR-34a-3p	1.24 (0.69, 2.23)	0.5	1.03 (0.57, 1.86)	0.9	0.77 (0.54, 1.09)	0.1	).56 (0.28, 1.14)	0.1
hsa-miR-34a-5p	0.92 (0.32, 2.62)	0.9	0.48 (0.00, 5552.36)	0.9	0.81 (0.53, 1.24)	0.3	.12 (0.57, 2.18)	0.7
hsa-miR-34c-5p	1.41 (0.75, 2.65)	0.3	0.86 (0.44, 1.68)	0.7	1.11 (0.85, 1.45)	0.5	).71 (0.40, 1.25)	0.2
hsa-miR-361-5p	0.49 (0.21, 1.12)	0.1	0.59 (0.28, 1.28)	0.2	0.76 (0.57, 1.02)	0.1	.05 (0.66, 1.67)	0.8
hsa-miR-3613-3p	0.90 (0.50, 1.60)	0.7	0.49 (0.27, 0.89)	0.02	0.96 (0.72, 1.30)	0.8	.27 (0.82, 1.98)	0.3
hsa-miR-3615	0.80 (0.41, 1.55)	0.5	0.36 (0.21, 0.62)	####	1.03 (0.79, 1.36)	0.8	).86 (0.55, 1.33)	0.5
hsa-miR-362-3p	1.17 (0.67, 2.05)	0.6	1.00 (0.51, 1.97)	0.9	0.84 (0.63, 1.12)	0.2	).80 (0.48, 1.34)	0.4
hsa-miR-363-3p	1.53 (0.87, 2.72)	0.1	1.14 (0.50, 2.60)	0.8	0.83 (0.62, 1.11)	0.2	).64 (0.36, 1.12)	0.1
hsa-miR-365a-3p-	0.99 (0.59, 1.66)	0.9	0.42 (0.21, 0.86)	0.02	0.99 (0.77, 1.26)	0.9	).70 (0.46, 1.07)	0.1
hsa-miR-374a-5p	1.01 (0.49, 2.06)	0.9	0.44 (0.22, 0.88)	0.02	1.01 (0.73, 1.39)	0.9	.17 (0.77, 1.77)	0.5
hsa-miR-374b-5p-	0.74 (0.39, 1.38)	0.3	0.85 (0.45, 1.57)	0.6	0.88 (0.68, 1.14)	0.4	).93 (0.56, 1.53)	0.8
hsa-miR-375	0.58 (0.28, 1.20)	0.1	0.44 (0.24, 0.80)	0.01	0.94 (0.70, 1.27)	0.7	.16 (0.73, 1.83)	0.5
hsa-miR-376a-3p	0.86 (0.43, 1.71)	0.7	0.54 (0.24, 1.25)	0.2	0.69 (0.51, 0.93)	0.02	).54 (0.27, 1.09)	0.1
hsa-miR-376b-3p	0.84 (0.44, 1.61)	0.6	0.51 (0.27, 0.96)	0.04	0.98 (0.74, 1.31)	0.9	.39 (0.87, 2.24)	0.2
hsa-miR-376c-3p	1.01 (0.57, 1.80)	0.9	0.68 (0.35, 1.33)	0.3	0.83 (0.63, 1.10)	0.2	).95 (0.57, 1.59)	0.9
hsa-miR-377-3p	1.00 (0.60, 1.67)	0.9	1.38 (0.81, 2.35)	0.2	0.94 (0.68, 1.31)	0.7	).78 (0.47, 1.31)	0.4
hsa-miR-378a-3p	0.85 (0.38, 1.93)	0.7	0.45 (0.22, 0.92)	0.03	0.95 (0.72, 1.26)	0.7	).98 (0.56, 1.73)	0.9
hsa-miR-378a-5p	1.27 (0.60, 2.66)	0.5	1.05 (0.44, 2.51)	0.9	0.83 (0.53, 1.31)	0.4	).75 (0.33, 1.73)	0.5
hsa-miR-381-3p	1.32 (0.71, 2.44)	0.4	1.07 (0.52, 2.21)	0.9	1.15 (0.87, 1.53)	0.3	).73 (0.37, 1.46)	0.4
hsa-miR-382-3p	1.56 (0.83, 2.96)	0.2	1.19 (0.62, 2.30)	0.6	1.25 (0.92, 1.72)	0.2	).68 (0.35, 1.33)	0.3
hsa-miR-409-3p	0.89 (0.40, 1.97)	0.8	0.69 (0.31, 1.54)	0.4	0.68 (0.42, 1.11)	0.1	).97 (0.48, 1.97)	0.9
hsa-miR-409-5p	1.16 (0.63, 2.13)	0.6	1.74 (0.95, 3.18)	0.1	0.93 (0.67, 1.29)	0.7	).79 (0.47, 1.31)	0.4
hsa-miR-411-3p	0.77 (0.20, 2.99)	0.7	0.32 (0.00, 1.05e+16)	0.9	0.82 (0.46, 1.45)	0.5	0.00, 1.67e+06)	0.9
hsa-miR-423-3p	1.18 (0.55, 2.52)	0.7	0.85 (0.43, 1.68)	0.6	0.91 (0.71, 1.17)	0.5	).82 (0.49, 1.37)	0.4
hsa-miR-423-5p	0.88 (0.36, 2.13)	0.8	0.51 (0.22, 1.18)	0.1	1.05 (0.68, 1.62)	0.8	).98 (0.43, 2.27)	0.9
hsa-miR-424-3p	1.28 (0.41, 4.00)	0.7	--	--	0.78 (0.37, 1.65)	0.5	0.00, 8.17e+10)	0.9
hsa-miR-424-5p	0.78 (0.38, 1.62)	0.5	0.41 (0.22, 0.78)	0.01	0.95 (0.67, 1.34)	0.8	).95 (0.52, 1.72)	0.9
hsa-miR-425-3p	0.87 (0.44, 1.73)	0.7	0.43 (0.22, 0.84)	0.01	0.95 (0.71, 1.27)	0.7	.20 (0.73, 1.98)	0.5
hsa-miR-425-5p	0.68 (0.40, 1.16)	0.2	0.72 (0.37, 1.40)	0.3	0.90 (0.68, 1.20)	0.5	).88 (0.47, 1.64)	0.7
hsa-miR-432-5p	0.95 (0.55, 1.66)	0.9	1.81 (1.12, 2.95)	0.02	0.94 (0.72, 1.23)	0.6	).98 (0.57, 1.71)	0.9
hsa-miR-433-3p	1.08 (0.57, 2.08)	0.8	0.74 (0.41, 1.34)	0.3	1.01 (0.72, 1.41)	0.9	).95 (0.56, 1.61)	0.9
hsa-miR-4429	0.80 (0.38, 1.68)	0.6	0.45 (0.22, 0.93)	0.03	0.89 (0.67, 1.17)	0.4	.04 (0.66, 1.62)	0.9
hsa-miR-4433a-5p	0.61 (0.31, 1.21)	0.2	0.73 (0.25, 2.15)	0.6	0.64 (0.44, 0.93)	0.02	.37 (0.83, 2.25)	0.2
hsa-miR-4433b-3p	0.82 (0.35, 1.92)	0.7	1.32 (0.53, 3.29)	0.6	1.03 (0.69, 1.52)	0.9	).81 (0.28, 2.32)	0.7
hsa-miR-4433b-5p	0.70 (0.32, 1.57)	0.4	0.41 (0.21, 0.78)	0.01	0.90 (0.55, 1.48)	0.7	).70 (0.36, 1.34)	0.3
hsa-miR-4446-3p	0.89 (0.37, 2.14)	0.8	0.48 (0.20, 1.12)	0.1	0.90 (0.53, 1.52)	0.7	).72 (0.26, 2.03)	0.5
hsa-miR-451a	2.79 (0.84, 9.22)	0.1	0.44 (0.00, 7915.53)	0.9	0.90 (0.42, 1.91)	0.8	0.00, 8.90e+09)	0.9
hsa-miR-452-5p	0.67 (0.18, 2.56)	0.6	0.55 (0.00, 1.74e+12)	0.9	0.86 (0.43, 1.68)	0.7	0.00, 1.39e+06)	0.9
hsa-miR-454-3p	0.25 (0.09, 0.71)	0.01	0.32 (0.00, 1.74e+16)	0.9	0.77 (0.34, 1.74)	0.5	0.00, 1.40e+06)	0.9
hsa-miR-4732-5p	0.90 (0.44, 1.82)	0.8	0.29 (0.10, 0.89)	0.03	0.76 (0.53, 1.09)	0.1	.40 (0.86, 2.27)	0.2
hsa-miR-4770	0.68 (0.39, 1.21)	0.2	0.92 (0.52, 1.63)	0.8	0.87 (0.64, 1.16)	0.3	).84 (0.51, 1.40)	0.5
hsa-miR-483-3p	0.81 (0.38, 1.72)	0.6	0.75 (0.39, 1.45)	0.4	0.81 (0.57, 1.14)	0.2	.07 (0.65, 1.75)	0.8

hsa-miR-483-5p	1.15 (0.74, 1.79)	0.5	0.93 (0.53, 1.62)	0.8	1.18 (0.86, 1.61)	0.3	.82 (0.43, 1.53)	0.5
hsa-miR-484	0.81 (0.26, 2.48)	0.7	0.54 (0.00, 9249.62)	0.9	1.04 (0.52, 2.08)	0.9	0.00, 2.55e+10)	0.9
hsa-miR-485-3p	0.75 (0.30, 1.87)	0.5	0.48 (0.18, 1.30)	0.1	0.99 (0.68, 1.45)	0.9	.99 (0.53, 1.85)	0.9
hsa-miR-486-3p	1.29 (0.64, 2.59)	0.5	1.06 (0.58, 1.95)	0.8	1.12 (0.77, 1.63)	0.5	.84 (0.41, 1.70)	0.6
hsa-miR-486-5p	--	--	1.09 (0.00, 1.35e+15)	0.9	1.80 (0.58, 5.57)	0.3	0.00, 1.77e+15)	0.9
hsa-miR-487b-3p	1.20 (0.57, 2.53)	0.6	0.56 (0.24, 1.33)	0.2	0.83 (0.60, 1.14)	0.2	.88 (0.44, 1.73)	0.7
hsa-miR-494-3p	1.18 (0.57, 2.44)	0.7	1.24 (0.60, 2.56)	0.6	0.84 (0.63, 1.11)	0.2	.57 (0.33, 0.97)	0.04
hsa-miR-495-3p	0.66 (0.28, 1.54)	0.3	0.82 (0.40, 1.67)	0.6	0.73 (0.51, 1.03)	0.1	.52 (0.91, 2.53)	0.1
hsa-miR-496	--	--	0.39 (0.00, 1.73e+15)	0.9	1.25 (0.62, 2.50)	0.5	0.00, 1.09e+09)	0.9
hsa-miR-497-5p	0.99 (0.46, 2.12)	0.9	0.55 (0.25, 1.20)	0.1	0.93 (0.69, 1.25)	0.6	.21 (0.68, 2.16)	0.5
hsa-miR-500a-3p	1.17 (0.59, 2.33)	0.7	0.49 (0.00, 9.55e+07)	0.9	0.92 (0.56, 1.51)	0.7	.00, 222109.50)	0.9
hsa-miR-501-3p	--	--	--	--	1.00 (0.49, 2.03)	0.9	0.00, 1.46e+09)	0.9
hsa-miR-502-3p	0.33 (0.10, 1.06)	0.1	--	--	0.97 (0.40, 2.36)	0.9	0.00, 1.15e+14)	0.9
hsa-miR-503-5p	1.53 (0.66, 3.56)	0.3	0.38 (0.00, 1.01e+12)	0.9	0.77 (0.44, 1.35)	0.4	.88 (1.07, 3.32)	0.03
hsa-miR-505-3p	0.61 (0.27, 1.38)	0.2	0.64 (0.31, 1.32)	0.2	0.76 (0.55, 1.04)	0.1	.91 (0.55, 1.53)	0.7
hsa-miR-519b-5p-	0.92 (0.46, 1.84)	0.8	0.58 (0.28, 1.17)	0.1	1.01 (0.74, 1.39)	0.9	.29 (0.78, 2.12)	0.3
hsa-miR-532-3p	0.81 (0.46, 1.43)	0.5	0.93 (0.49, 1.78)	0.8	0.94 (0.68, 1.30)	0.7	.17 (0.63, 2.18)	0.6
hsa-miR-532-5p	0.74 (0.44, 1.25)	0.3	0.79 (0.39, 1.61)	0.5	1.18 (0.91, 1.54)	0.2	.28 (0.78, 2.11)	0.3
hsa-miR-542-3p	0.79 (0.41, 1.53)	0.5	0.40 (0.22, 0.74)	0	0.95 (0.71, 1.27)	0.7	.98 (0.61, 1.56)	0.9
hsa-miR-543	0.84 (0.28, 2.51)	0.8	0.66 (0.28, 1.58)	0.4	0.90 (0.58, 1.39)	0.6	.67 (0.31, 1.47)	0.3
hsa-miR-545-5p	0.93 (0.39, 2.25)	0.9	0.25 (0.00, 6.31e+13)	0.9	0.77 (0.44, 1.36)	0.4	0.00, 2.10e+06)	0.9
hsa-miR-548e-3p	1.11 (0.64, 1.95)	0.7	2.56 (1.36, 4.81)	0	1.04 (0.79, 1.37)	0.8	.86 (0.53, 1.39)	0.5
hsa-miR-550a-3p	2.02 (0.87, 4.68)	0.1	0.86 (0.40, 1.85)	0.7	1.11 (0.75, 1.63)	0.6	.67 (0.31, 1.46)	0.3
hsa-miR-564	1.18 (0.69, 2.00)	0.6	1.31 (0.75, 2.29)	0.3	1.16 (0.85, 1.57)	0.4	.64 (0.37, 1.14)	0.1
hsa-miR-574-3p	0.88 (0.46, 1.72)	0.7	0.71 (0.30, 1.70)	0.4	1.09 (0.73, 1.63)	0.7	.00 (0.55, 1.83)	0.9
hsa-miR-576-5p	0.82 (0.29, 2.33)	0.7	0.23 (0.00, 6.81e+14)	0.9	0.89 (0.48, 1.65)	0.7	.46 (0.59, 3.63)	0.4
hsa-miR-582-3p	0.80 (0.43, 1.49)	0.5	1.12 (0.56, 2.22)	0.8	0.97 (0.73, 1.30)	0.8	.06 (0.62, 1.81)	0.8
hsa-miR-582-5p	0.62 (0.30, 1.32)	0.2	0.32 (0.11, 0.90)	0.03	1.09 (0.76, 1.57)	0.6	.22 (0.76, 1.97)	0.4
hsa-miR-584-5p	0.91 (0.33, 2.55)	0.9	0.62 (0.23, 1.65)	0.3	0.79 (0.55, 1.13)	0.2	.85 (0.45, 1.60)	0.6
hsa-miR-589-5p	0.95 (0.50, 1.79)	0.9	1.61 (0.75, 3.43)	0.2	0.94 (0.65, 1.34)	0.7	.14 (0.65, 2.00)	0.7
hsa-miR-590-3p	0.87 (0.30, 2.49)	0.8	0.42 (0.00, 5.19e+11)	0.9	0.92 (0.53, 1.62)	0.8	.97 (0.36, 2.65)	0.9
hsa-miR-590-5p	1.11 (0.56, 2.20)	0.8	0.79 (0.43, 1.46)	0.4	0.79 (0.57, 1.08)	0.1	.19 (0.69, 2.06)	0.5
hsa-miR-596	0.60 (0.19, 1.90)	0.4	0.18 (0.00, 1.96e+14)	0.9	0.76 (0.38, 1.50)	0.4	.00, 143909.75)	0.9
hsa-miR-598-3p	0.70 (0.16, 2.99)	0.6	0.57 (0.00, 6.05e+10)	0.9	0.65 (0.30, 1.41)	0.3	0.00, 33806.89)	0.9
hsa-miR-613	0.97 (0.45, 2.12)	0.9	1.13 (0.00, 37622.94)	0.9	0.91 (0.57, 1.46)	0.7	.40 (0.13, 1.28)	0.1
hsa-miR-616-5p	1.02 (0.58, 1.80)	0.9	2.93 (1.56, 5.50)	0	1.06 (0.81, 1.39)	0.7	.93 (0.54, 1.59)	0.8
hsa-miR-624-5p	0.83 (0.26, 2.66)	0.7	0.32 (0.00, 1.15e+15)	0.9	0.92 (0.45, 1.91)	0.8	0.00, 1.39e+06)	0.9
hsa-miR-625-3p	0.88 (0.36, 2.13)	0.8	0.56 (0.22, 1.39)	0.2	0.71 (0.50, 1.00)	0.1	.26 (0.72, 2.21)	0.4
hsa-miR-627-5p	1.36 (0.76, 2.42)	0.3	1.41 (0.71, 2.81)	0.3	1.08 (0.78, 1.49)	0.6	.84 (0.43, 1.64)	0.6
hsa-miR-628-3p	0.77 (0.42, 1.43)	0.4	0.36 (0.19, 0.67)	0	0.96 (0.73, 1.28)	0.8	.94 (0.59, 1.50)	0.8
hsa-miR-642a-5p	1.10 (0.59, 2.04)	0.8	2.25 (1.27, 3.97)	0.01	0.95 (0.73, 1.23)	0.7	.88 (0.50, 1.55)	0.7
hsa-miR-6511b-3p	1.22 (0.54, 2.72)	0.6	0.72 (0.35, 1.47)	0.4	0.91 (0.63, 1.31)	0.6	.88 (0.52, 1.49)	0.6
hsa-miR-652-3p	1.09 (0.60, 1.98)	0.8	1.21 (0.62, 2.37)	0.6	0.79 (0.56, 1.12)	0.2	.70 (0.39, 1.27)	0.2
hsa-miR-652-5p	1.17 (0.59, 2.34)	0.7	1.45 (0.61, 3.45)	0.4	1.20 (0.75, 1.90)	0.5	.00, 166352.07)	0.9
hsa-miR-654-3p	0.64 (0.18, 2.29)	0.5	0.32 (0.00, 2.68e+15)	0.9	1.50 (0.82, 2.76)	0.2	.43 (0.60, 3.39)	0.4
hsa-miR-654-5p	0.81 (0.29, 2.28)	0.7	--	--	1.79 (1.04, 3.07)	0.04	.04 (0.36, 3.02)	0.9

hsa-miR-656-3p	1.31 (0.73, 2.35)	0.4	0.26 (0.13, 0.52)	####	1.22 (0.93, 1.61)	0.2	.06 (0.65, 1.73)	0.8
hsa-miR-659-3p	0.37 (0.10, 1.41)	0.1	0.89 (0.00, 35953.72)	0.9	1.09 (0.70, 1.69)	0.7	.58 (0.87, 2.88)	0.1
hsa-miR-660-5p	0.72 (0.34, 1.49)	0.4	0.61 (0.33, 1.14)	0.1	0.81 (0.63, 1.04)	0.1	.07 (0.65, 1.75)	0.8
hsa-miR-664a-3p	0.85 (0.46, 1.56)	0.6	1.22 (0.63, 2.38)	0.6	1.02 (0.75, 1.39)	0.9	.90 (0.50, 1.64)	0.7
hsa-miR-664a-5p	--	--	0.57 (0.00, 8.58e+09)	0.9	0.76 (0.41, 1.42)	0.4	0.00, 6.55e+14)	0.9
hsa-miR-664b-3p	1.06 (0.55, 2.03)	0.9	1.99 (0.86, 4.57)	0.1	0.97 (0.69, 1.38)	0.9	.88 (0.52, 1.49)	0.6
hsa-miR-6803-3p	0.36 (0.10, 1.29)	0.1	--	--	0.65 (0.33, 1.30)	0.2	.42 (0.55, 3.69)	0.5
hsa-miR-7-1-3p	1.03 (0.36, 2.98)	0.9	0.49 (0.00, 1.35e+10)	0.9	0.81 (0.41, 1.59)	0.5	.99 (0.37, 2.64)	0.9
hsa-miR-7-5p	1.04 (0.28, 3.92)	0.9	0.77 (0.00, 163392.81)	0.9	1.28 (0.76, 2.17)	0.4	.22 (0.45, 3.33)	0.7
hsa-miR-744-5p	1.66 (0.96, 2.88)	0.1	1.07 (0.59, 1.93)	0.8	0.92 (0.70, 1.22)	0.6	.71 (0.44, 1.17)	0.2
hsa-miR-766-3p	0.58 (0.31, 1.10)	0.1	0.83 (0.42, 1.61)	0.6	0.89 (0.63, 1.27)	0.5	.98 (0.55, 1.74)	0.9
hsa-miR-769-5p	0.96 (0.52, 1.77)	0.9	1.30 (0.73, 2.34)	0.4	0.86 (0.63, 1.17)	0.3	.09 (0.64, 1.86)	0.8
hsa-miR-7977	1.34 (0.65, 2.77)	0.4	0.52 (0.28, 0.95)	0.03	0.73 (0.54, 0.97)	0.03	.13 (0.64, 1.99)	0.7
hsa-miR-877-3p	0.49 (0.15, 1.62)	0.20	0.77 (0.00, 1.53e+13)	0.9	1.02 (0.57, 1.85)	0.9	.02 (0.30, 3.49)	0.9
hsa-miR-877-5p	0.10 (0.05, 0.21)	####	0.48 (0.00, 5.51e+07)	0.9	0.79 (0.47, 1.33)	0.4	.85 (0.86, 3.96)	0.1
hsa-miR-885-5p	1.52 (0.79, 2.91)	0.2	1.22 (0.63, 2.40)	0.6	0.78 (0.59, 1.04)	0.1	.87 (0.48, 1.56)	0.6
hsa-miR-9-3p	0.85 (0.29, 2.44)	0.8	--	--	1.11 (0.64, 1.92)	0.7	0.00, 3.83e+08)	0.9
hsa-miR-92a-3p	1.27 (0.42, 3.87)	0.7	0.58 (0.00, 2.51e+08)	0.9	1.10 (0.57, 2.13)	0.8	0.00, 5.77e+13)	0.9
hsa-miR-92b-3p	0.79 (0.39, 1.58)	0.5	0.59 (0.31, 1.13)	0.1	1.05 (0.82, 1.35)	0.7	.27 (0.78, 2.06)	0.3
hsa-miR-93-3p	1.29 (0.65, 2.53)	0.5	0.35 (0.00, 2.84e+09)	0.9	1.48 (1.08, 2.04)	0.02	.63 (0.34, 1.18)	0.2
hsa-miR-93-5p	0.77 (0.25, 2.40)	0.7	0.68 (0.00, 20659.62)	0.90	0.84 (0.45, 1.56)	0.6	.67 (0.23, 1.91)	0.5
hsa-miR-941	1.17 (0.65, 2.12)	0.6	3.06 (1.65, 5.67)	####	1.03 (0.80, 1.32)	0.8	.94 (0.57, 1.55)	0.8
hsa-miR-942-5p	0.50 (0.15, 1.71)	0.3	0.95 (0.31, 2.93)	0.9	1.20 (0.74, 1.97)	0.5	.01 (0.49, 2.07)	0.9
hsa-miR-95-3p	0.76 (0.24, 2.37)	0.6	0.65 (0.00, 3.84e+12)	0.9	0.78 (0.35, 1.76)	0.6	.21 (0.42, 3.49)	0.7
hsa-miR-96-5p	0.23 (0.09, 0.56)	0	0.70 (0.21, 2.32)	0.6	0.94 (0.54, 1.66)	0.8	0.00, 61235.23)	0.9
hsa-miR-98-3p	0.71 (0.19, 2.66)	0.6	0.25 (0.00, 5.48e+15)	0.9	0.71 (0.37, 1.36)	0.3	.34 (1.27, 4.32)	0.01
hsa-miR-98-5p	0.77 (0.33, 1.82)	0.6	0.45 (0.20, 1.00)	0.1	0.93 (0.67, 1.28)	0.6	.91 (0.49, 1.69)	0.8
hsa-miR-99a-5p	0.74 (0.42, 1.33)	0.3	0.61 (0.34, 1.10)	0.1	0.85 (0.62, 1.16)	0.3	.08 (0.69, 1.69)	0.7
hsa-miR-99b-5p	0.71 (0.38, 1.33)	0.3	0.98 (0.41, 2.35)	0.9	0.82 (0.62, 1.08)	0.2	.51 (0.29, 0.90)	0.02
PIR12151	--	--	0.10 (0.00, 9.99e+13)	0.9	1.45 (0.36, 5.84)	0.6	0.00, 1.43e+14)	0.9
PIR1340	1.00 (0.57, 1.77)	0.9	1.05 (0.59, 1.86)	0.9	0.87 (0.69, 1.10)	0.3	.79 (0.49, 1.29)	0.3
PIR20101	1.20 (0.52, 2.75)	0.7	0.56 (0.30, 1.05)	0.1	1.05 (0.75, 1.48)	0.8	.12 (0.62, 2.00)	0.7
PIR2096	1.02 (0.34, 3.10)	0.9	0.34 (0.00, 1.87e+10)	0.9	1.31 (0.86, 2.00)	0.2	.98 (0.37, 2.56)	0.9
PIR212993	1.32 (0.57, 3.03)	0.5	0.43 (0.00, 660095.43)	0.9	1.12 (0.67, 1.87)	0.7	.55 (0.79, 3.05)	0.2
PIR218424	1.82 (0.46, 7.23)	0.4	0.35 (0.00, 3.11e+15)	0.9	1.57 (0.88, 2.82)	0.1	0.00, 4.38e+10)	0.9
PIR2229	1.59 (0.84, 2.99)	0.2	0.78 (0.36, 1.69)	0.5	1.09 (0.73, 1.63)	0.7	.05 (0.58, 1.91)	0.9
PIR22527	1.02 (0.57, 1.85)	0.9	0.35 (0.10, 1.25)	0.1	1.06 (0.78, 1.44)	0.7	.97 (0.54, 1.73)	0.9
PIR227919	1.25 (0.63, 2.46)	0.5	1.09 (0.44, 2.72)	0.8	0.94 (0.55, 1.60)	0.8	.47 (0.15, 1.49)	0.2
PIR23216	0.66 (0.23, 1.90)	0.4	0.64 (0.00, 25103.98)	0.9	1.12 (0.72, 1.75)	0.6	.13 (0.57, 2.21)	0.7
PIR232882	0.78 (0.48, 1.25)	0.3	0.81 (0.47, 1.41)	0.5	0.82 (0.61, 1.11)	0.2	.37 (0.83, 2.26)	0.2
PIR243353	0.69 (0.39, 1.22)	0.2	0.83 (0.48, 1.42)	0.5	0.98 (0.71, 1.35)	0.9	.38 (0.84, 2.27)	0.2
PIR248758	0.98 (0.50, 1.89)	0.9	0.63 (0.28, 1.42)	0.3	0.96 (0.68, 1.38)	0.8	.58 (0.99, 2.53)	0.1
PIR251099	1.36 (0.52, 3.58)	0.5	0.43 (0.00, 2.94e+13)	0.9	0.76 (0.46, 1.26)	0.3	0.00, 1.48e+07)	0.9
PIR265711	0.69 (0.37, 1.30)	0.3	0.84 (0.45, 1.59)	0.6	1.02 (0.76, 1.37)	0.9	.43 (0.91, 2.25)	0.1
PIR2888	0.93 (0.30, 2.92)	0.9	0.49 (0.00, 5.59e+10)	0.9	2.22 (0.71, 6.90)	0.2	0.00, 1.83e+15)	0.9
PIR2962	0.87 (0.48, 1.56)	0.6	0.76 (0.39, 1.50)	0.4	1.08 (0.80, 1.45)	0.6	.24 (0.70, 2.22)	0.5

PIR31112	1.08 (0.58, 2.00)	0.8	0.65 (0.37, 1.16)	0.1	0.75 (0.56, 1.00)	0.1	.04 (0.65, 1.66)	0.9
PIR32212	0.68 (0.28, 1.66)	0.4	0.99 (0.00, 1.86e+08)	0.9	0.81 (0.41, 1.59)	0.5	0.00, 4.27e+09)	0.9
PIR32519	0.83 (0.48, 1.46)	0.5	0.69 (0.37, 1.30)	0.2	0.70 (0.51, 0.97)	0.03	.27 (0.78, 2.07)	0.3
PIR32636	1.29 (0.56, 3.00)	0.6	1.11 (0.35, 3.52)	0.9	0.88 (0.57, 1.35)	0.6	.58 (0.23, 1.49)	0.3
PIR32637	1.43 (0.63, 3.25)	0.4	1.29 (0.38, 4.40)	0.7	0.92 (0.55, 1.53)	0.8	.83 (0.32, 2.14)	0.7
PIR33384	0.71 (0.41, 1.23)	0.2	0.85 (0.46, 1.56)	0.6	1.16 (0.90, 1.50)	0.2	.07 (0.63, 1.81)	0.8
PIR33872	0.94 (0.57, 1.56)	0.8	0.85 (0.46, 1.54)	0.6	0.95 (0.73, 1.23)	0.7	.06 (0.61, 1.83)	0.8
PIR36598	1.75 (0.49, 6.23)	0.4	0.84 (0.00, 2.05e+12)	0.9	1.01 (0.48, 2.14)	0.9	0.00, 5.01e+08)	0.9
PIR36667	0.71 (0.30, 1.66)	0.4	0.63 (0.27, 1.47)	0.3	1.04 (0.74, 1.47)	0.8	.87 (0.47, 1.62)	0.7
PIR36772	0.81 (0.44, 1.46)	0.5	0.63 (0.38, 1.06)	0.1	0.90 (0.67, 1.20)	0.5	.37 (0.84, 2.22)	0.2
PIR37355	2.04 (1.05, 3.94)	0.03	1.02 (0.36, 2.87)	0.9	0.88 (0.58, 1.33)	0.5	.57 (0.22, 1.46)	0.2
PIR38142	0.84 (0.27, 2.64)	0.8	1.28 (0.37, 4.41)	0.7	0.66 (0.35, 1.26)	0.2	0.00, 2.45e+12)	0.9
PIR40039	2.02 (0.78, 5.26)	0.1	1.75 (0.55, 5.55)	0.3	1.34 (0.64, 2.82)	0.4	0.00, 6.73e+09)	0.9
PIR40304	0.76 (0.39, 1.49)	0.4	0.87 (0.45, 1.70)	0.7	0.80 (0.56, 1.13)	0.2	.89 (0.59, 1.34)	0.6
PIR40506	1.36 (0.53, 3.49)	0.5	0.94 (0.00, 50300.49)	0.9	0.68 (0.36, 1.26)	0.2	.76 (0.24, 2.39)	0.6
PIR40766	1.98 (0.66, 5.92)	0.2	2.03 (0.00, 306723.78)	0.9	1.01 (0.55, 1.84)	0.9	0.00, 1.97e+14)	0.9
PIR41574	0.82 (0.25, 2.70)	0.7	0.48 (0.00, 1.00e+13)	0.9	0.79 (0.38, 1.63)	0.5	.34 (0.51, 3.56)	0.6
PIR41647	1.06 (0.58, 1.94)	0.8	0.85 (0.47, 1.56)	0.6	0.95 (0.70, 1.29)	0.7	.32 (0.80, 2.17)	0.3
PIR43147	0.40 (0.12, 1.41)	0.2	1.15 (0.00, 21414.72)	0.9	1.15 (0.71, 1.87)	0.6	.93 (0.35, 2.46)	0.9
PIR43376	0.69 (0.34, 1.38)	0.3	0.62 (0.33, 1.18)	0.1	0.74 (0.56, 0.99)	0.04	.06 (0.62, 1.81)	0.8
PIR44080	1.21 (0.35, 4.16)	0.8	0.39 (0.00, 4.78e+15)	0.9	0.69 (0.24, 1.95)	0.5	0.00, 1.04e+15)	0.9
PIR45809	0.71 (0.22, 2.34)	0.6	0.85 (0.35, 2.07)	0.7	0.90 (0.59, 1.36)	0.6	.94 (0.43, 2.05)	0.9
PIR46251	1.29 (0.37, 4.49)	0.7	1.35 (0.00, 1.15e+07)	0.9	0.55 (0.18, 1.67)	0.3	.62 (0.57, 4.60)	0.4
PIR46358	1.52 (0.44, 5.24)	0.5	0.43 (0.00, 3.01e+16)	0.9	1.52 (0.75, 3.12)	0.2	0.00, 15232.50)	0.9
PIR48383	0.77 (0.39, 1.53)	0.5	0.76 (0.42, 1.39)	0.4	0.89 (0.66, 1.21)	0.5	.00 (0.43, 2.35)	0.9
PIR49867	1.32 (0.50, 3.51)	0.6	0.46 (0.00, 1.17e+11)	0.9	0.66 (0.35, 1.23)	0.2	(0.00, 5211.22)	0.9
PIR49916	1.09 (0.59, 2.03)	0.8	1.15 (0.57, 2.34)	0.7	0.96 (0.69, 1.32)	0.8	.46 (0.83, 2.56)	0.2
PIR51124	1.18 (0.60, 2.30)	0.6	0.74 (0.41, 1.36)	0.3	0.84 (0.60, 1.18)	0.3	.59 (0.35, 0.99)	0.05
PIR51374	0.69 (0.33, 1.44)	0.3	0.67 (0.24, 1.87)	0.4	0.92 (0.64, 1.32)	0.6	.89 (0.44, 1.79)	0.7
PIR52468	0.77 (0.26, 2.30)	0.6	0.45 (0.00, 7585.15)	0.9	0.63 (0.42, 0.95)	0.03	.63 (0.30, 1.32)	0.2
PIR54042	0.66 (0.22, 1.97)	0.5	0.62 (0.00, 5.64e+14)	0.9	1.40 (0.31, 6.25)	0.7	0.00, 1.04e+15)	0.9
PIR54043	0.71 (0.24, 2.15)	0.5	0.74 (0.00, 1.25e+15)	0.9	2.09 (0.58, 7.56)	0.3	0.00, 1.53e+15)	0.9
PIR54782	0.86 (0.29, 2.53)	0.8	1.58 (0.00, 72472.38)	0.9	0.96 (0.60, 1.54)	0.9	.18 (0.46, 3.02)	0.7
PIR55662	1.07 (0.42, 2.74)	0.9	0.47 (0.00, 2.14e+09)	0.9	1.27 (0.80, 2.01)	0.3	.03 (0.49, 2.17)	0.9
PIR56396	1.11 (0.36, 3.43)	0.9	0.56 (0.00, 1.70e+13)	0.9	0.99 (0.58, 1.67)	0.9	0.00, 12663.02)	0.9
PIR57322	0.69 (0.40, 1.19)	0.2	0.74 (0.37, 1.47)	0.4	0.89 (0.65, 1.21)	0.5	.45 (0.76, 2.77)	0.3
PIR57387	1.66 (0.76, 3.65)	0.2	0.59 (0.00, 1.04e+09)	0.9	0.62 (0.37, 1.04)	0.1	.98 (0.30, 3.24)	0.9
PIR57403	0.81 (0.44, 1.49)	0.5	0.72 (0.42, 1.23)	0.2	0.85 (0.63, 1.13)	0.3	.85 (0.52, 1.41)	0.5
PIR57576	0.90 (0.51, 1.56)	0.7	0.85 (0.48, 1.51)	0.6	0.82 (0.63, 1.07)	0.1	.03 (0.63, 1.69)	0.9
PIR57581	0.77 (0.43, 1.36)	0.4	0.64 (0.35, 1.17)	0.1	0.81 (0.63, 1.05)	0.1	.29 (0.76, 2.18)	0.3
PIR58593	0.40 (0.14, 1.20)	0.1	1.28 (0.35, 4.69)	0.7	1.07 (0.63, 1.79)	0.8	0.00, 4.81e+08)	0.9
PIR58596	0.72 (0.44, 1.19)	0.2	0.70 (0.37, 1.32)	0.3	0.90 (0.65, 1.25)	0.5	.20 (0.72, 1.99)	0.5
SNO1209	0.89 (0.41, 1.94)	0.8	1.06 (0.38, 2.99)	0.9	0.79 (0.50, 1.25)	0.3	.45 (0.15, 1.40)	0.2
SNO1210	0.83 (0.46, 1.50)	0.5	1.05 (0.54, 2.04)	0.9	1.36 (0.99, 1.87)	0.1	.63 (0.39, 1.04)	0.1
SNO1257	1.16 (0.37, 3.69)	0.8	0.54 (0.00, 3.39e+10)	0.9	0.89 (0.51, 1.55)	0.7	0.00, 8.39e+15)	0.9
SNO1277	0.88 (0.28, 2.72)	0.8	0.57 (0.26, 1.22)	0.1	0.68 (0.42, 1.09)	0.1	.65 (0.27, 1.55)	0.3

SNO1289	0.80 (0.29, 2.17)	0.7	0.67 (0.00, 1.44e+07)	0.9	0.93 (0.54, 1.58)	0.8	0.00, 1.88e+09)	0.9
SNO1290	0.77 (0.25, 2.38)	0.6	0.46 (0.00, 8.74e+09)	0.9	0.80 (0.50, 1.29)	0.4	.85 (0.32, 2.31)	0.8
SNO1291	0.36 (0.11, 1.16)	0.1	0.49 (0.00, 1.13e+10)	0.9	0.83 (0.53, 1.29)	0.4	.52 (0.17, 1.60)	0.3
SNO1374	0.75 (0.41, 1.35)	0.3	0.68 (0.33, 1.40)	0.3	0.85 (0.62, 1.17)	0.3	.76 (0.44, 1.28)	0.3
SNO1382	0.47 (0.14, 1.64)	0.2	0.87 (0.00, 75025.30)	0.9	1.00 (0.66, 1.52)	0.9	0.00, 1.40e+09)	0.9
SNO1384	0.88 (0.47, 1.65)	0.7	0.53 (0.24, 1.19)	0.1	0.92 (0.63, 1.36)	0.7	.11 (0.61, 2.04)	0.7
SNO1387	0.96 (0.57, 1.62)	0.9	1.65 (0.81, 3.36)	0.2	1.21 (0.94, 1.55)	0.1	.76 (0.44, 1.31)	0.3
SNO1394	0.36 (0.12, 1.04)	0.1	0.58 (0.22, 1.57)	0.3	0.99 (0.72, 1.37)	0.9	.16 (0.64, 2.11)	0.6
SNO1399	1.19 (0.46, 3.06)	0.7	1.12 (0.00, 46996.25)	0.9	1.20 (0.67, 2.16)	0.5	0.00, 3.62e+06)	0.9
SNO1401	0.65 (0.35, 1.20)	0.20	0.88 (0.44, 1.77)	0.7	0.94 (0.71, 1.24)	0.6	.15 (0.61, 2.19)	0.7
SNO1403	0.13 (0.05, 0.31)	####	1.01 (0.36, 2.82)	0.9	1.08 (0.65, 1.80)	0.8	.70 (0.31, 1.56)	0.4
SNO1405	0.93 (0.47, 1.83)	0.8	0.37 (0.00, 5365.19)	0.8	0.96 (0.69, 1.33)	0.8	.78 (0.32, 1.89)	0.6
SNO1407	0.37 (0.10, 1.42)	0.1	1.39 (0.56, 3.47)	0.5	0.82 (0.46, 1.46)	0.5	.87 (0.39, 1.95)	0.7
SNO1408	0.80 (0.27, 2.37)	0.7	0.56 (0.20, 1.56)	0.3	0.78 (0.43, 1.41)	0.4	.83 (0.24, 2.85)	0.8
SNO1409	0.56 (0.20, 1.60)	0.3	0.50 (0.15, 1.67)	0.3	0.90 (0.48, 1.67)	0.7	0.00, 2.97e+08)	0.9
SNO1413	0.56 (0.25, 1.26)	0.2	0.46 (0.18, 1.16)	0.1	0.95 (0.72, 1.24)	0.7	.83 (0.44, 1.57)	0.6
SNO1414	0.59 (0.31, 1.11)	0.1	1.38 (0.77, 2.46)	0.3	0.76 (0.56, 1.04)	0.1	.89 (0.55, 1.45)	0.6
SNO1417	1.14 (0.59, 2.20)	0.7	0.95 (0.40, 2.27)	0.9	1.11 (0.77, 1.61)	0.6	.55 (0.26, 1.15)	0.1
SNO1426	0.62 (0.31, 1.25)	0.2	0.70 (0.39, 1.26)	0.2	1.04 (0.80, 1.36)	0.8	.81 (0.50, 1.30)	0.4
SNO1441	0.88 (0.27, 2.84)	0.8	1.95 (0.00, 1.90e+13)	0.9	1.50 (0.75, 2.99)	0.3	.07 (0.38, 3.04)	0.9
SNO1457	0.74 (0.37, 1.51)	0.4	1.13 (0.60, 2.11)	0.7	1.08 (0.82, 1.42)	0.6	.85 (0.48, 1.50)	0.6
SNO1458	0.75 (0.43, 1.29)	0.3	0.85 (0.47, 1.54)	0.6	0.84 (0.63, 1.12)	0.2	.33 (0.75, 2.36)	0.3
SNO1460	0.69 (0.40, 1.18)	0.2	0.92 (0.48, 1.78)	0.8	1.40 (0.99, 1.99)	0.1	.84 (0.48, 1.46)	0.5
SNO1465	0.27 (0.09, 0.80)	0.02	0.42 (0.00, 1.49e+16)	0.9	1.76 (1.05, 2.96)	0.03	0.00, 1.97e+15)	0.9
SNO1466	0.89 (0.29, 2.75)	0.8	0.80 (0.00, 2.66e+09)	0.9	1.10 (0.54, 2.25)	0.8	--	--
SNO1472	0.74 (0.42, 1.30)	0.3	0.71 (0.40, 1.27)	0.2	0.94 (0.72, 1.23)	0.7	.98 (0.56, 1.72)	0.9
SNO1490	--	--	--	--	1.71 (0.83, 3.55)	0.1	0.00, 2.77e+14)	0.9
SNO1502	0.95 (0.56, 1.62)	0.9	0.89 (0.49, 1.63)	0.7	0.95 (0.70, 1.30)	0.8	.90 (0.52, 1.58)	0.7
SNO1507	1.00 (0.44, 2.25)	0.9	0.58 (0.21, 1.58)	0.3	1.13 (0.74, 1.71)	0.6	.47 (0.21, 1.08)	0.1
SNO1549	0.26 (0.12, 0.57)	0	0.35 (0.00, 1.78e+15)	0.9	1.10 (0.59, 2.06)	0.8	0.00, 1.14e+11)	0.9
SNO1550	1.28 (0.61, 2.65)	0.5	1.15 (0.67, 2.00)	0.6	1.14 (0.82, 1.58)	0.4	.70 (0.39, 1.27)	0.2
SNO1562	0.30 (0.13, 0.71)	0.01	0.53 (0.00, 1.02e+15)	0.9	0.79 (0.33, 1.90)	0.6	0.00, 3.60e+10)	0.9
SNO1563	1.15 (0.55, 2.38)	0.7	0.85 (0.40, 1.82)	0.7	1.39 (1.02, 1.91)	0.04	.60 (0.27, 1.35)	0.2
SNO1568	0.90 (0.31, 2.58)	0.8	1.28 (0.58, 2.85)	0.5	1.03 (0.67, 1.56)	0.9	(0.00, 4377.97)	0.8

OR (95% CI) indicates odds ratio and 95% confidence intervals estimated from adjusted logistic regression models of prevalent disease and HR (95% CI) indicates hazard ratio and 95% confidence intervals estimated from adjusted Cox proportional hazards models of incident disease. All models containing terms for CVD risk factors described in methods and listed in Table 1.

Supplemental Table IV. Clincal factors associated with expression of select exRNAs

	exRNA Associated with Prevalent Stroke								exRNA Associated with Incident Stroke					
	hsa-miR-877-5p		hsa-miR-124-3p		hsa-miR-320d		SNO1403		hsa-miR-656-3p		hsa-miR-3615		hsa-miR-941	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	0.97 (0.85, 1.12)	0.7	0.98 (0.82, 1.16)	0.8	0.87 (0.72, 1.05)	0.1	0.96 (0.85, 1.09)	0.6	0.90 (0.82, 0.97)	0.01	0.98 (0.89, 1.08)	0.7	1.04 (0.96, 1.13)	0.3
Sex (Female)	0.82 (0.61, 1.08)	0.2	0.97 (0.73, 1.29)	0.8	1.14 (0.83, 1.56)	0.4	0.76 (0.58, 0.98)	0.04	0.85 (0.72, 1.01)	0.1	0.92 (0.79, 1.07)	0.3	1.12 (0.94, 1.34)	0.2
SBP	1.14 (0.97, 1.33)	0.1	1.12 (0.96, 1.30)	0.1	1.17 (1.00, 1.38)	0.1	1.11 (0.95, 1.30)	0.2	1.02 (0.91, 1.15)	0.7	1.02 (0.91, 1.14)	0.7	0.93 (0.84, 1.04)	0.2
DBP	1.00 (0.83, 1.20)	0.9	0.92 (0.80, 1.06)	0.3	0.86 (0.72, 1.04)	0.1	0.90 (0.77, 1.05)	0.2	1.01 (0.91, 1.12)	0.9	1.05 (0.94, 1.16)	0.4	1.05 (0.95, 1.16)	0.3
Triglycerides	0.93 (0.79, 1.10)	0.4	1.02 (0.86, 1.22)	0.8	0.91 (0.76, 1.09)	0.3	0.94 (0.76, 1.17)	0.6	1.03 (0.93, 1.15)	0.5	1.02 (0.92, 1.14)	0.7	1.07 (0.95, 1.20)	0.3
Total:HDL Cholesterol	1.01 (0.87, 1.17)	0.9	1.15 (1.00, 1.32)	0.1	1.19 (1.00, 1.42)	0.1	1.12 (0.94, 1.34)	0.2	0.97 (0.88, 1.08)	0.6	0.97 (0.87, 1.08)	0.6	0.90 (0.80, 1.00)	0.05
C-reactive protein	1.05 (0.91, 1.22)	0.5	1.04 (0.88, 1.23)	0.6	1.13 (0.99, 1.29)	0.1	0.95 (0.85, 1.07)	0.4	1.03 (0.95, 1.11)	0.4	1.06 (0.97, 1.17)	0.2	1.00 (0.91, 1.09)	0.9
Diabetes	0.97 (0.61, 1.53)	0.9	0.75 (0.45, 1.23)	0.3	0.90 (0.55, 1.47)	0.7	1.09 (0.70, 1.69)	0.7	0.96 (0.76, 1.21)	0.7	0.87 (0.65, 1.16)	0.3	1.05 (0.82, 1.35)	0.7
Glucose	0.72 (0.57, 0.93)	0.01	1.06 (0.84, 1.33)	0.6	0.78 (0.65, 0.95)	0.01	0.90 (0.74, 1.08)	0.3	0.83 (0.74, 0.94)	0.003	0.95 (0.84, 1.07)	0.4	1.16 (1.01, 1.33)	0.04
A1C	1.31 (0.99, 1.72)	0.1	1.00 (0.83, 1.20)	0.9	1.11 (0.89, 1.38)	0.3	1.11 (0.88, 1.41)	0.4	1.13 (1.01, 1.27)	0.03	1.17 (1.03, 1.33)	0.02	0.85 (0.74, 0.98)	0.02
Current Smoker	1.04 (0.60, 1.80)	0.9	1.23 (0.78, 1.96)	0.4	0.94 (0.53, 1.66)	0.8	1.44 (0.93, 2.23)	0.1	1.28 (1.01, 1.61)	0.04	1.06 (0.82, 1.37)	0.7	1.03 (0.78, 1.36)	0.8
Aspirin 3/week	0.98 (0.75, 1.29)	0.9	1.15 (0.91, 1.46)	0.2	1.13 (0.83, 1.55)	0.4	1.01 (0.79, 1.30)	0.9	1.00 (0.82, 1.23)	0.9	0.95 (0.83, 1.10)	0.5	1.01 (0.83, 1.24)	0.9
Antihypertensive Rx	1.00 (0.84, 1.21)	0.9	0.91 (0.68, 1.21)	0.5	1.26 (0.97, 1.63)	0.1	0.78 (0.55, 1.08)	0.1	0.94 (0.78, 1.12)	0.5	0.96 (0.79, 1.17)	0.7	1.07 (0.90, 1.29)	0.4
Lipid Lowering Rx	0.93 (0.69, 1.25)	0.6	0.83 (0.65, 1.05)	0.1	0.98 (0.74, 1.30)	0.9	0.93 (0.70, 1.23)	0.6	0.99 (0.83, 1.18)	0.9	0.93 (0.79, 1.09)	0.4	1.02 (0.86, 1.21)	0.8