Supplemental Material

Table S1. MiRNAs with largest fold changes between Responders and Non-Responders to TZD therapy in the discovery cohort.

MiRNA	mean of ΔCt in R	mean of ΔCt in NR	ΔΔCt	FC
hsa-miR-142-3p	0.93	-1.88	2.81	0.14
hsa-miR-30e-3p*	2.99	0.65	2.34	0.20
hsa-miR-16	-1.82	-3.50	1.68	0.31
hsa-miR-26b	2.35	0.67	1.68	0.31
hsa-miR-126	-3.11	-4.67	1.56	0.34
hsa-miR-140	4.07	2.53	1.55	0.34
hsa-miR-885-5p	2.10	0.59	1.51	0.35
hsa-miR-30d-5p	1.38	-0.11	1.49	0.36
hsa-miR-29a	3.75	2.37	1.39	0.38
hsa-miR-10a	5.86	4.54	1.32	0.40
hsa-miR-199a-3p	1.84	0.54	1.30	0.41
hsa-miR-10b#	2.35	4.54	-2.19	4.57
hsa-let-7g-5p	1.02	3.51	-2.49	5.62
hsa-miR-193b*	1.63	4.14	-2.51	5.71
hsa-miR-376c	3.83	6.36	-2.53	5.76
hsa-miR-483-5p	0.85	3.76	-2.91	7.53
hsa-miR-197*	-0.13	2.79	-2.92	7.58
hsa-miR-134*	2.85	5.96	-3.11	8.63
hsa-miR-423-5p*	1.25	4.46	-3.21	9.28

FC= Fold change; R= Responders to TZD therapy, NR= Non-responders to TZD therapy; * = Mann U test p-value <0.05; $\Delta\Delta Ct = (Ct_R — Ct_{mean}) — (Ct_{NR} — Ct_{mean})$

Table-S2. Differential miRNA expression by ancestry.

	Unadjusted model			Adjusted Model		
Variable	**Coefficient**	**p-value**	**BH Adjusted p-value**	**Coefficient**	**p-value**	**BH Adjusted p-value**
let-7g-5p	**-1.03**	**9.8e-06**	**0.00012**	**-1.2496724**	**5.32E-06**	**3.19E-05**
miR-126	0.8	0.12	0.199	**1.5794077**	**7.80E-03**	**0.019**
miR-126-5p	**1.29**	**7.9e-05**	**0.00047**	**1.261008**	**9.77E-04**	**0.002931**
miR-142-3p	-0.018	0.98	0.988	-0.3277406	7.38E-01	0.81
miR-16	**-0.81**	**0.006**	**0.024**	**-1.834635**	**7.34E-09**	**8.81e-08**
miR-199a-3p	0.31	0.18	0.278	0.3608554	1.78E-01	0.31
miR-26b	-0.92	0.08	0.188	-1.3191166	3.09E-02	0.062
miR-29a	-0.005	0.98	0.988	0.3419071	4.13E-01	0.57
miR-30d-5p	0.88	0.017	0.052	0.2259936	5.92E-01	0.71
miR-376c	-0.80	0.10	0.199	-0.4615756	4.24E-01	0.57
miR-423-5p	0.32	0.3	0.399	**1.3137803**	**5.57E-05**	**0.00022**
miR-885-5p	-0.016	0.97	0.988	0.1097881	8.44E-01	0.84

BH= Benjamini-Hochberg

Model: miRNA expression = ancestry + age + sex+ Study;

Compared microRNA expression between European Americans (n=100 total from GERA and PEAR-2) and African Americans (n=50 from PEAR-1)

Table S3. **DBP response modelled with miRNA expression in HCTZ treated European American cohort from GERA.**

Covariates	miRNA	Estimate	SE	P-Val	R-squared	Adjusted R-squared	Model AIC
Unadjusted	miR-193b	1.25	0.61	0.046	0.08	0.06	379.23
Age, sex adjusted		1.75	0.57	0.0038	0.29	0.24	371.11
Baseline BP, age, sex adjusted		1.8	0.57	0.0028	**0.32**	**0.26**	**370.78**
Unadjusted	miR-30d-5p	-2.29	1.05	0.034	0.09	0.07	378.68
Age, sex adjusted		-2.19	0.99	0.032	0.22	0.17	375.30
Baseline BP, age, sex adjusted		-2.11	0.99	0.04	**0.24**	**0.17**	**376.08**
Clinical model	Baseline BP	-0.5041	0.4269	0.24	0.16	0.11	378.86
	Age	-0.6336	0.2836	0.03			
	Sex	4.0914	3.5874	0.26			

Table S4. **SBP response modelled with miRNA expression in HCTZ treated European American cohort from GERA.**

Covariates	**miRNA**	**Estimate**	**SE**	**P-Val**	**R-squared**	**Adjusted R-squared**	**Model AIC**
Unadjusted	miR-193b	2.49	0.82	0.004	0.16	0.15	408.08
Age, sex adjusted		3.25	0.75	0.00008	0.40	0.36	396.21
Baseline BP, age, sex adjusted		3.069	0.71	8.9e-05	**0.47**	**0.43**	**391.91**
Unadjusted	miR-30d-5p	-4.29	1.42	0.004	0.16	0.15	408.09
Age, sex adjusted		-4.14	1.34	0.0034	0.29	0.25	403.98
Baseline BP, age, sex adjusted		-3.73	1.29	6.2e-03	**0.37**	**0.31**	**400.78**
Clinical model	Baseline BP Age Sex	-0.52 -0.69 4.65	0.21 0.38 4.81	0.018 0.08 0.34	**0.25**	**0.19**	**407.24**

Table S5. DBP response modelled with miRNA expression in CTD treated European American cohort in PEAR-2.

	Variable	Estimate	SE	P-Val	R-squared	Adjusted R-squared	Model AIC
Unadjusted	let-7g-5p	2.4	0.764	0.003	0.18	0.16	332.18
Age, sex adjusted		1.99	0.76	0.013	0.26	0.21	331.14
Baseline BP, age, sex adjusted		1.68	0.79	0.04	**0.29**	**0.22**	**331.13**
Unadjusted	miR-142-3p	-0.63	0.23	0.009	0.14	0.12	334.32
Age, sex adjusted		-0.54	0.23	0.02	0.24	0.19	332.33
Baseline BP, age, sex adjusted		-0.49	0.22	0.04	**0.29**	**0.23**	**330.92**
Unadjusted	miR-423-5p	1.68	0.62	0.009	0.14	0.12	334.37
Age, sex adjusted		1.44	0.61	0.022	0.24	0.19	332.22
Baseline BP, age, sex adjusted		1.19	0.62	0.06	**0.28**	**0.21**	**331.96**
Clinical model	Baseline BP Age Sex	-0.51 -0.35 4.32	0.26 0.15 2.15	0.05 0.019 0.05	0.21	0.16	333.9

Figure S1. Frequency of subjects with detected plasma microRNA count in the discovery cohort.

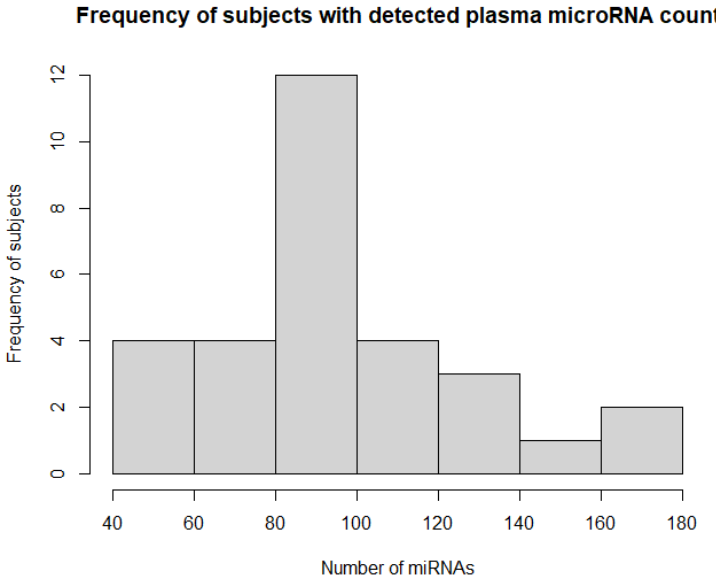
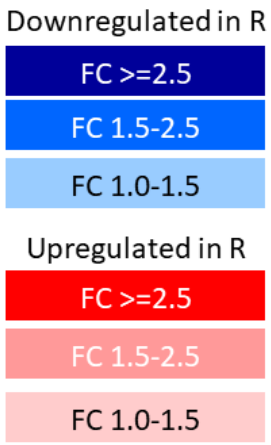


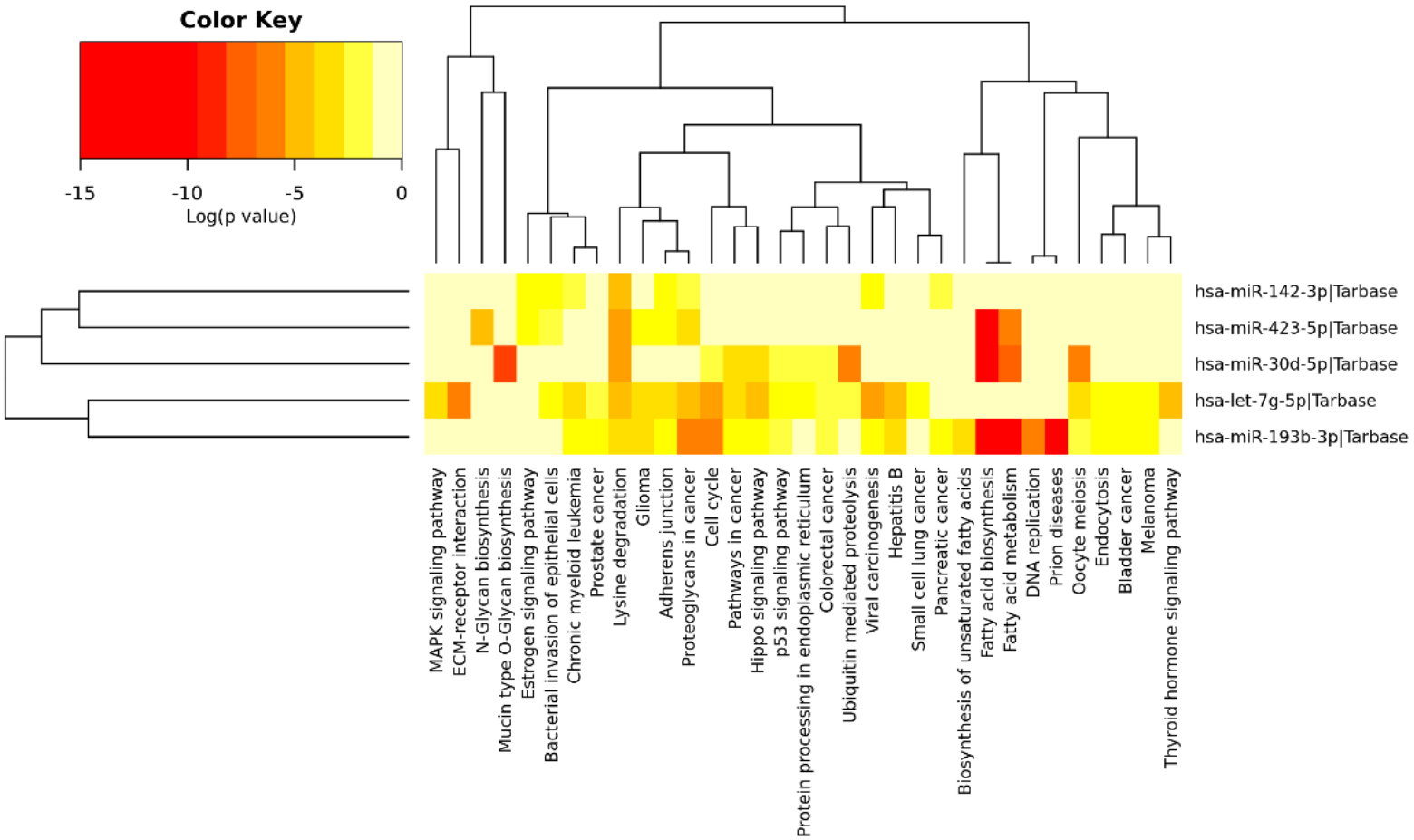
Figure S2. FC for the list of 19 miRNAs that were taken forward for replication/validation.

MiRNA	Discovery	GERA-1	PEAR-2	PEAR-1AA	Combined Analysis
hsa-miR-142-3p	0.14	0.52	0.071	0.57	0.21
hsa-miR-30e-3p	0.2				
hsa-miR-26b	0.31	0.84	0.53	0.48	0.80
hsa-miR-16	0.31	1.07	1.76	1.09	1.36
hsa-miR-126	0.34	0.88	0.68	0.74	0.83
hsa-miR-140	0.34				
hsa-miR-885-5p	0.35	1.49	2.53	1.25	1.66
hsa-miR-30d-5p	0.36	0.51	0.633	0.68	0.69
hsa-miR-29a	0.38	1.13	1.54	0.6	1.13
hsa-miR-10a	0.4				
hsa-miR-199a-3p	0.41	1.26	1.62	1.52	1.44
hsa-miR-10b#	4.57				
hsa-let-7g-5p	5.62	1.28	2.51	1.38	1.59
hsa-miR-193b	5.71	2.73	0.88		
hsa-miR-376c	5.76	0.75	0.92	1.45	0.92
hsa-miR-483-5p	7.53				
hsa-miR-197	7.58				
mmu-miR-134	8.63				
hsa-miR-423-5p	9.28	1.028	2.91	1.37	1.58



Combined analysis= Analysis combining all three qPCR datasets i.e., from GERA-1, PEAR-2, PEAR-1 AA.

Figure S3. Pathway analysis for predicted mRNA/gene targets of identified miRNAs.



Among the pathways enriched by the predicted target genes, lysine degradation, fatty acid biosynthesis and fatty acid metabolism were the most significant ones (with least p-values) with relevance to hypertension. All 5 microRNAs (miR-142-3p, 423-5p, 30d-5p, 7g-5p and 193b-3p) are involved in lysine degradation, and only 3 miRNAs (423-5p, 30d-5p and 193b-3p) in fatty acid biosynthesis and metabolism pathways.