

Supplemental Table S1. Anthropometric, hematological, hematochemical, molecular, oxidative stress parameters and smoking habits.

Variable (unit of measurement)	(a) Young adults (22-50 y.o.) N=19, M=7, W=12	(b) Adults (51-70 y.o.) N=28, M=14, W=14	(c) Older adults (71-99 y.o.) N=20, M=13, W=7	(d) Ultra- centenarians (100-111 y.o.) N=11, M=2, W=9	P
BMI	21.60 (17.30-30.20) N=19, (22.49±3.57) M=7, (25.21±2.52) W=12, (20.90±3.14)	27.20 (21.40-35.40) N=27, (27.29±3.32) M=14, (27.41±2.61) W=13, (27.15±4.05)	29.00 (18.70-40.90) N=20, (28.84±5.59) M=13, (28.82±4.72) W=7, (28.86 ±7.37)	22.30 (18.40-29.70) N=10, (22.95±3.09) M=2, (26.10±5.09) W=8, (22.16 ±2.25)	a vs b,c d vs b,c
Hematochemical parameter					
CRP (mg/dL, <5)	0.63 (0.16-23.23) N=19, (2.67±5.54) M=7, (0.60±0.55) W=12, (3.88±6.76)	1.68 (0.42-63.86) N=27, (4.32±11.97) M=14, (5.90±16.71) W=13, (2.61±1.41)	1.10 (0.23-26.75) N=20 (3.19±5.88) M=13, (3.40±7.07) W=7, (2.79±3.03)	1.92 (1.13-5.97) N=11, (2.62±1.57) M=2, (3.36±0.45) W=9, (2.45±1.70)	ns
Molecular test					
RTL	1.19 (0.95-1.51) N=19, (1.20±1.74) M=7, (1.12±0.20) W=12, (1.25±0.15)	1.05 (0.68-1.31) N=27 (0.99±0.16) M=14, (0.98±0.17) W=13, (1.00±0.14)	0.69 (0.45-1.19) N=20, (0.74±0.19) M=13, (0.73±0.16) W=7, (0.76±0.25)	0.73 (0.47-0.85) N=10, (0.70±0.12) M=2, (0.67±0.12) W=8, (0.71±0.13)	a vs b,c,d b vs c,d
Oxidative stress parameters					
PON (U/L)	122.81 (40.63- 392.43) N=19, (149.63±91.62) M=7, (136.39±75.73) W=12, (157.36±102.13)	91.42 (43.40-300.09) N=27, (112.41±62.84) M=14, (115.88±74.57) W=13, (108.67±50.04)	100.65 (19.39- 222.53) N=19, (99.28±57.82) M=12, (106.49±62.23) W=7, (86.93±51.48)	78.02 (43.40-254.85) N=10, (105.26±72.61) M=2, (137.58±96.63) W=8, (97.19±71.21)	ns
TEAC (mM)	3601.24 (2589.58- 4721.66) N=19, (3577.83±463.34)	3794.43 (1805.68- 5485.35) N=27, (3784.18±686.92)	3574.19 (2819.23- 5572.38) N=19, (3764.02±718.84)	3650.68 (2967.68- 4658.10) N=10, (3725.91±502.69)	ns

	M=7, (3523.58±653.98) W=12, (3609.47±339.18) <u>2.61 (1.19-4.52)</u> N=19, (2.76±1.02) M=7, (3.23±0.84) W=12, (2.48±1.04)	M=14, (3837.36±839.79) W=13, (3726.92±501.50) <u>2.62 (0.95-4.45)</u> N=27, (2.67±1.03) M=14, (2.62±0.92) W=13, (2.71±1.17)	M=12, (3596.05±572.30) W=7, (4051.99±892.50) <u>2.84 (0.64-4.18)</u> N=19, (2.63±1.02) M=12, (2.98±0.95) W=7, (2.04±0.91)	M=2, (3812.89±1195.31) W=8, (3704.17±343.64) <u>2.55 (1.12-5.78)</u> N=10, (2.77±1.37) M=2, (2.55±0.25) W=8, (2.82±1.55)	ns
Smoking habits					
Smoker	N=5, 26.32% M=2, 28.57% W=3, 25.00%	N=7, 29.19% M=2, 18.18% W=5, 38.46%	N=3, 15.00% M=3, 23.08% W=0, 0%	N=0, 0% M=0, 0% W=0, 0%	
Ex-smoker	N=2, 10.53% M=0, 0% W=2, 16.67%	N=10, 41.67% M=6, 54.55% W=4, 30.77%	N=10, 50.0% M=8, 61.54% W=2, 28.57%	N=0, 0% M=0, 0% W=0, 0%	p=0.001*
Never smoked	N=12, 63.16% M=5, 71.43 W=7, 58.33%	N=7, 29.17% M=3, 27.27% W=4, 30.77%	N=7, 35.00% N=2, 15.38% W=5, 71.43%	N=11, 100% M=2, 100% W=9, 100%	

Abbreviations: y.o.=years old; N=total number of cases; M=men; W=women; SD=standard deviation; BMI=body mass index; CRP=C-reactive protein; RTL=relative telomere length; PON=paraoxonase; TEAC=trolox equivalent antioxidant capacity; MDA=malondialdehyde.

Data underlined are the median (min-max) of the total number of cases. Data between round brackets are mean values ± SD.

a, b, c, and d indicate, respectively, young adults, adults, older adults, and LLIs.

The table shows the pairwise comparisons between the different groups, *i.e.*, a, b, c, d. p-value≤0.05 is considered significant; ns=not significant.

Bonferroni test is used for pairwise comparisons.

*To test if there is difference in the smoking habit for Age Class is used the Fisher's exact test.

Data are presented both as median, minimum, maximum values, and mean±standard deviation (SD). For continuous variables, the one-way Analysis of Variance (ANOVA) is used to test if age produces a significant effect on the parameters. The Fisher test is considered to evaluate the significance of the results. For each statistically significant effect, we conduct a post hoc multiple comparison test using Bonferroni method. For categorical variables, we consider the chi-squared test or the Fisher exact test to compare differences between groups of age. All analyses were performed using Stata version 16.1 and all hypothesis testing are considered statistically significant for p≤ 0.05.

Supplemental Table S2. KEGG pathway of miR-21-5p and miR-126-3p.

KEGG pathway	Predicted miR-21-5p target genes	Predicted miR-126-3p target genes
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hsa04022_cGMP-PKG_signaling_pathway	OPRD1 KCNMA1 EDNRA ATF2 CALML4 PIK3R3 SOD2 PIK3R3 PIK3R3 APH1B	ATP2B4 CALML4 ADCY1 MYLK3 ROCK2 INPP5K INPP5B DGKB ATF2 ADCY1 PPARGC1A HDAC2EIF4EBP DVL1 HDAC2	CREB5 PDE5A MEF2D MEF2C DGKD IPPK DGKH PPIP5K2 CREB5 FOXO3 FOXO3 DTX4 DTX3L
hsa04070_Phosphatidylinositol_signaling_system			
hsa04211_Longevity_regulating_pathway			
hsa04213_Longevity_regulating_pathway			
hsa04330_Notch_signaling_pathwa			

Top 5 enriched KEGG pathway clustered by validated targets of miR-21-5p and miR-126-3p and corresponding target genes.

Supplemental Table S3. REACTOME pathway of miR-21-5p and miR-126-3p.

REACTOME pathway	Predicted miR-21-5p target genes	Predicted miR-126-3p target genes
R-HSA-9614085_FOXO-mediated transcription	CITED2 PPARGC1A SMAD4 SOD2 YWHAZ	RBL2 BCL6 FOXO3
R-HSA-400253_Circadian Clock	ARNTL ATF2 CLOCK HDAC2 PPARGC1A	CREM CRTIC1 MEF2C MEF2D
R-HSA-9615017_FOXO-mediated transcription of oxidative stress	PPARGC1A	FOXO3 PLXNA4
R-HSA-9013148_CDC42 GTPase cycle	ARHGAP31 GIT2 PAK3 SH3PXD2A	ARAP2 ARHGAP35 ARHGAP42 CDC42BPA FARP1 FNBP1L IQGAP1 MCF2L
R-HSA-449147_Signaling by Interleukins	BRWD1 HDAC2 ITGB2 PIK3R3 PPIA PSMD8 PSMF1 RAP1B SOD2 SRGAP1 STAT5A	OPRD1 PSD8 SOD2 STAT5A

TOLLIPUBE2V1
WIPF2 YWHAZ

Top 5 enriched REACTOME pathway clustered by validated targets of miR-21-5p and miR-126-3p and corresponding target genes.

Supplemental Table S4. KEGG pathway of miR-146a-5p and miR-181a-5p.

KEGG pathway	Predicted miR-146a-5p target genes			Predicted miR-181a-5p target genes		
hsa05205_Proteoglycans_in_cancer	CBL	ERBB4	FZD1	ANK3	CAMK2D	
		FZD8	HSPG2		CCND1	
		IHH	IQGAP1		CDKN1A	
			MAPK13		ESR1	FZD5
		MSN	PIK3CA		HPSE2	ITPR2
		PLCE1	PPP1R12B			PRKACB
			PRKACA		RAC1	TP53
			PRKGCSMAD2			WNT5A
			WNT16			
		ERBB4	GRIN2A		ADORA2B	
hsa04020_Calcium_signaling_pathway		HTR2C	ITPKB		CACNA1B	
		MYLK3	NOS1		CALM1	
		PHKA2	PLCD3		CAMK2D	
		PLCE1	PRKACA		ITPR2	ORAI2
			PRKGCG			PHKG2
		BPNT2	CDS1	INPP4B		PRKACB
			ITPKB	MTMR14		
hsa04070_Phosphatidylinositol_signaling_system			MTMR8		CALM1	ITPR2
			PIK3CA			MTMR7
		PLCE1	PRKGCG		PPIP5K1	
			SLC8A1			PTEN
		HDAC2	ORC4	RBX1		
hsa04110_Cell_cycle			SMAD2	SMC1A	ABL1	CCND1
				TFDP2		CDC6
						CDKN1A

		SKP2	SMC1B
		TP53	
		CALM1	CAMK2D
		CDC27	CPEB3
	MAPK13	PGR	ITPR2
hsa04114_Oocyte_meiosis	PPP2R5E		PRKACB
	PRKACA		RPS6KA6
	RBX1	SMC1A	SKP1
			SMC1B
			SPDYE11
			SPDYE17

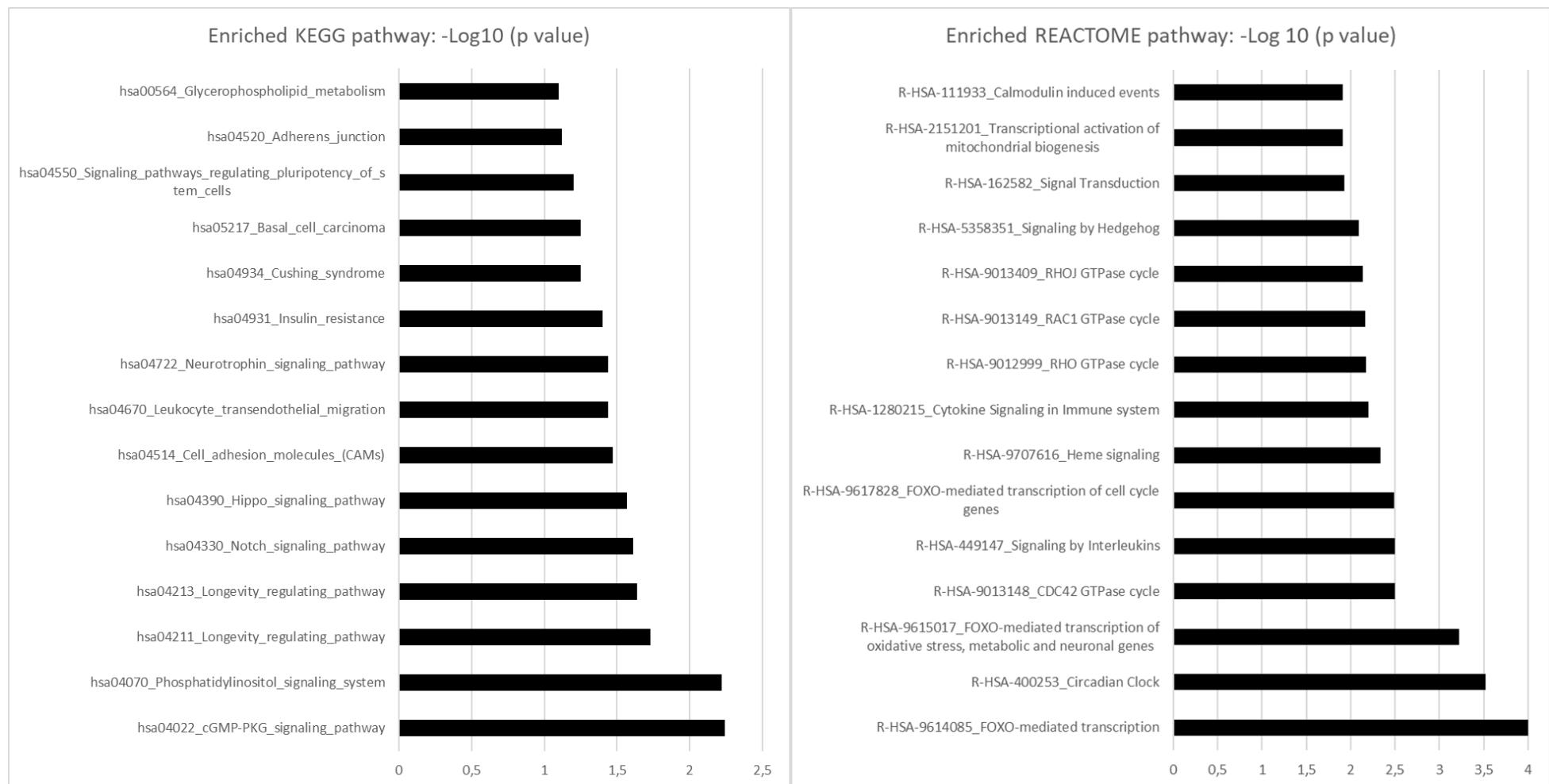
Top 5 enriched KEGG pathway clustered by validated targets of miR-146a-5p and miR-181a-5p and corresponding target genes.

Supplemental Table S5. REACTOME pathway of miR-146a-5p and miR-181a-5p.

REACTOME pathway	Predicted miR-146a-5p target genes			Predicted miR-181a-5p target genes		
R-HSA-4090294_SUMOylation of intracellular receptors	PGR	SUMO3UBE2I		VDR	ESR1	NR1I2 PPARA
	ARHGEF7	CACNB2	EPB41	CACNA1B	CALM1CAMK2D	
	ERBB4	GLUL	KCNQ5KCNS1	CHRNA9	GLRA2	
	KCNS2	LRRTM2	NCALD	GNAI2	GRIP2	KCND3
	NLGN3NPTN	PPFIA1	PPFIBP2	KCNJ6	KCNK10,	
	PPM1E	PRKAB2	PRKACA	LIN7C	LRFN2	NTRK3
	PRKAR2B	PRKGCGSLC1A2		PRKACB	RAC1	
	SLC38A2	SLC6A11		RPS6KA6	SLC1A3	
	SLC6A4	SLITRK4		SLC1A7	SLC6A1	
	TSPOAP1	GRIN2A	KCNA2	SNAP25	SYN2	
	KCNK7DLG2	LRRC49		SYT2	GRIN2A	KCNA2
	ARHGEF7	CACNB2	ERBB4	CACNA1B	CALM1CAMK2D	
	GLUL	GRIN2A	NCALD	CHRNA9	GLRA2	
		PPFIA1	PPM1E PRKAB2		GNAI2	GRIN2B
		PRKACA	PRKAR2B DLG2		GRIP2	KCNJ6 LIN7C
		PRKGCGSLC1A2	SLC38A2		NPTN	PRKACB
		SLC6A11	SLC6A4		RAC1	RPS6KA6
		TSPOAP1			SLC1A3	SLC1A7
R-HSA-112316_Neuronal System						
R-HSA-112315_Transmission across Chemical Synapses						

		SLC6A1	SNAP25
		SYN2	DLG2
R-HSA-3232118_SUMOylation of transcription factors	PIAS1 UBE2I SUMO3TFAP2A	FOXL2 PIAS2 TP53BP1	
R-HSA-3215018_Processing and activation of SUMO	SUMO3UBE2I	SENP2	

Top 5 enriched REACTOME pathway clustered by validated targets of miR-146a-5p and miR-181a-5p and corresponding target genes.



Supplemental Figure S1. The top 15 enriched KEGG and REACTOME pathways from predicted target genes of miR-21-5p and miR-126-3p searched by miRWalk.



Supplemental Figure S2. The top 15 enriched KEGG and REACTOME pathways from predicted target genes of miR-146a-5p and miR-181a-5p searched by miRWalk.