

Supplementary Table 1 : Circulating miRNA profiling studies included in this analysis

*min & max values; IFG= Impaired fasting glucose ; IGT= Impaired glucose tolerance

Authors	Years	Countries	Patient studied	Ages	Sex (M/F)	BMI Kg/m2_	HbA1c %	Fasting glucose g/L
Prabu P.	2015	INDIA	T2DM vs control	44.4±8.1	25/24	25.7±3.50	7.8±1.60	2.65±0.62
			Prediabetes vs controls	44.1±7.0	23/24	24.9±2.90	6.3±0.80	1.91±0.32
Liu Y.	2014	CHINA	T2DM vs controls	50.2±6.7	78/82	23.32±0.31	9.16±1.64	2.04±0.48
			Prediabetes vs controls	47.9±7.8	82/75	23.10±0.26	6.25±0.67	0.93±0.11
Parrizas M.	2014	SPAIN	T2DM vs controls	55.7±1.37	NR	30.1±0.7	NR	1.23±0.43
			Prediabetes IFG vs controls	53.6±0.1	NR	29.4±0.7 ¹	NR	1.09±0.13
			Prediabetes ITG vs controls	56.8±1.4		28.9±0.8 ²		0.90±0.18
Zampetaki A.	2010	UK	Physical activity	53.8±3.4	NR	27.3±1.3	NR	1.01±0.73
			T2DM vs control	66.3±8.9	30/50	28.0±4.4	6.5±1.4	1.39±0.50
Zhang T.	2013	CHINA	T2DM vs control	63±8.5	16/14			1.96±0.53
			Prediabetes vs controls	62±8	9/21	NR	NR	1.17±0.04
Higuchi C	2015	JAPAN	T2DM vs control	62.3±13.2	96/59	25.9±4.9	7.31±1.1	NR
Karolina D.S.	2011	SINGAPOR E	T2DM vs control	41.0±12.1	13/0	28.0±4.9	NR	1.91±0.77
			Pre diabetes vs control	48.0±10.4	8/0	30.0±3.9	NR	1.08±0.02
Karolina D.S.	2012	SINGAPOR E	T2DM vs control	34.2±8.4	NR	26.5±5.9	NR	1.64±0.43
			Obese vs control	41.4±9.2	NR	34.5±4.9	NR	0.92±0.18
Ortega F.J.	2014	SPAIN	Obese T2DM vs obese	57.7±8	18/0	33.4±3.3	7.1±2.1	2.01±1.03
			Lean T2DM vs lean	54.0±10.0	30/0	26.4±2.4	7.7±1.5	2.12±0.61
			Metormine treatment	52.0±9.0	8/9	35.7±6.2	8.3±4.6	1.25±0.19
Kong L.	2011	CHINA	T2DM vs control	47.3±2.6	9/9	26.3±0.8	NR	1.58±0.09
			Pre diabetes vs control	49.3±2.8	11/8	26.7±0.9	NR	1.09±0.02
Wang X.	2014	SWEDEN	T2DM vs control	55.8±5.8	NR	NR	NR	NR
Rong Y.	2013	CHINA	T2DM vs control	48.5 (42.0-56.0)*	42/48	24.6±3.7	NR	1.34 (1.22-2.33)*
Santovito D.	2014	ITALY	T2DM vs control	57.2±9.6	12/6	31.6±5.1	9.6±1.5	1.46±0.30
Pescador N.	2013	SPAIN	T2DM vs control	42.9±12.3	7/6	22.7±2.4	NR	1.26±0.23
			Obese vs control	41.7±11.2	3/17	42.7±4.8	NR	0.93±0.063
Heneghan H.M.	2011	IRELAND	Obese vs control	42.0 (37.0-53.0)*	6/13	45.8 (43.0-52.0)*	6.1 (5.4-6.4)*	0.96 (0.85-1.14)*
Ortega FJ	2013	SPAIN	Obese (BMI>40) vs control	42.0±10.0	12/0	45.5±8.9	5.6±1.1	1.27±0.54
			Bariatric surgery	44.0±14.0	6/13	42.9±5.9	NR	NR
Wang R	2015	CHINA	Obese vs control	24.0±2.6	62/61	37.7±4.4	NR	0.95 ±0.16
Prats-Puig A	2013	SPAIN	Obese vs control	9.2±1.4	18/22	NR	NR	NR
Murri M	2013	SPAIN	Obese vs control	30.0±7.0	6/6	40.0±6.5	NR	0.97±0.85
Wang YT	2013	TAIWAN	Pre-diabetes vs control	56.5±8.5	16/15	26.6±3.6	NR	1.07±0.19
Zhao C	2011	CHINA	Gestational diabetes vs control	28.8±2.2	0/24	21.4±1.7	NR	0.96±0.16
Sawada S	2013	JAPAN	Physical activity	29.9±1.2	12/0	23.2±1.2	NR	NR
Mooren FC	2014	GERMANY	Physical activity	NR	13/0	NR	NR	NR
Baggish AL	2014	USA	Physical activity	51.8±1.4	21/0	NR	NR	NR
Uhlemann M	2012	GERMANY	Physical activity	30.4±2.0	7/6	23.4±1.1	NR	NR
Baggish AL	2011	USA	Physical activity	19.1±0.6	11/0	NR	NR	NR

Supplementary Table 2: Methods used for total RNA extraction, and miRNA detection

LT: LifeTechnologies; AB: Applied Biosystems

Studies	Samples	RNA-Extraction technologies	Kits for reverse transcription	Technologies used for miRNA detection
Zampetaki A.	Plasma	miR-Neasy-mini kit (Qiagen)	Megaplex Primer Pools	TaqMan miRNA assays (LT)
Prabu P.	Serum	miR-Neasy-mini kit (Qiagen)	miRCURY LNA™ power Labeling Kit (Exiqon)	miRCURY LNA™ PCR system (Exiqon)
Karolina D.S - 2011	Whole blood	RiboPure™-Blood kit (Ambion)	miRCURY LNA™ power Labeling Kit (Exiqon) MultiScribe-based high capacity cDNA	miRCURY LNA™ Arrays TaqMan miRNA assays (LT) (Validation)
Karolina D.S - 2012	Whole blood	RiboPure™-Blood kit (Ambion)	miRCURY LNA™ power Labeling Kit (Exiqon) MultiScribe-based high capacity cDNA	miRCURY LNA™ Arrays TaqMan miRNA assays (LT) (Validation)
Ortega F.J. - 2014	Plasma	miR-Vana™PARIS™ kit (LT)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan hydrolysis probe (LT)
Ortega F.J. - 2013	Plasma	miR-Vana™PARIS™ kit (LT)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan hydrolysis probe (LT)
Kong L.	Serum	miR-Vana™PARIS™ kit (LT)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan miRNA assays (LT)
Pescador N.	Serum	miR-Neasy-mini kit (Qiagen)	miRCURY LNA™ power Labeling Kit (Exiqon)	MicroRNA LNA™ PCR primer mix
Wang X.	Plasma	miR-Neasy-mini kit (Qiagen)	Universal cDNA synthesis kit (Exiqon)	MicroRNA LNA™ PCR primer mix
Rong Y.	Plasma	miR-Vana™PARIS™ kit (LT)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan miRNA assays (LT)
Santovito D.	Plasma (exosomes)	miR-Neasy-mini kit (Qiagen)	Quantitative real-time PCR (Exiqon)	Quantitative real-time PCR (Exiqon)
Heneghan H.M.	Whole blood	Phenol-chloroform	MultiScribe-based high capacity cDNA	TaqMan miRNA assays (LT)
Liu Y.	Serum	ND	Taqman MiRNA Reverse transcription kit (LT)	TaqMan miRNA assays (LT)
Parrizas M.	Serum	miR-Neasy-mini kit (Qiagen)	Quantitative real-time PCR (Exiqon)	Quantitative real-time PCR (Exiqon)
Wang R.	Serum	miR-Neasy-mini kit (Qiagen)	miRCURY LNA Universal RT Kit (Exiqon)	Quantitative real-time PCR (Exiqon)
Prats-Puig A.	Plasma	miR-Vana™PARIS™ kit (LT)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan hydrolysis probe ((LT)
Murri M.	Whole blood	miR-Neasy-mini kit (Qiagen)	StepOnePlus Real-Time PCR System	TaqMan miRNA assays (LT)
Wang YT	Serum	MasterPure™ complete DNA and RNA purification kit	Taqman MiRNA Reverse transcription kit (LT)	TaqMan miRNA assays (LT)
Zhang T	Plasma	Phenol-chloroform	RevertAid cDNA Synthetis Kit (Thermo)	SYBR Premix DimerEraser kit (TAKAEA)
Zhao C	Serum	miR-Neasy-mini kit (Qiagen)	Megaplex Primer Pools	TaqMan miRNA assays (LT)
Uhlemann M	Plasma	miR-Neasy-mini kit (Qiagen)	Taqman MiRNA Reverse transcription kit (LT)	TaqMan miRNA assays (LT)
Higuchi C	Serum	QiAamp Circulating Nucleic Acid kit (Qiagen)	Taqman MiRNA Reverse transcription kit (AB)	TaqMan miRNA assays (AB)
Sawada S	Serum	miRVana PARIS kit (Ambion)	Taqman MiRNA Reverse transcription kit (AB)	TaqMan miRNA assays (AB)
Mooren FC	Plasma	miR-Neasy-mini kit (Qiagen)	Taqman MiRNA Reverse transcription kit (AB)	TaqMan miRNA assays (AB)
Baggish AL - 2014	Plasma	microRNA extraction kit (Benevbio)	MicroRNA Assay kit	TaqMan miRNA assays (LT)
Baggish AL - 2011	Plasma	microRNA extraction kit (Benevbio)	MicroRNA Assay kit	TaqMan miRNA assays (LT)

Supplementary Table 3: Circulating miRNAs quantification in obese subjects vs controls, revalidated by individual RT-PCR assays

(+)= increased miRNA concentration in the blood of obese patients compared with controls;
 (-) = decreased miRNA concentration in the blood of obese patients compared with controls

References	Years	Countries	Number of obeses/controls	Samples	MicroRNAs	Status
Heneghan H.M.	2011	IRELAND	30/20	Blood	miR 17-5-p; miR 132	+
Ortega F.J.	2013	SPAIN	12/49	Plasma	miR-222;miR-140-5p;miR-142-3p;miR-126 miR-423-5p;miR -520c-3p;miR-532-5p;miR-125b;miR-130b;miR-221;miR-15a;miR-21;miR-590-5p;miR-193a-5p;miR-122;miR-483-5p;miR-636;miR-625	+ -
Prats-Puig A.	2013	SPAIN	40/85	Plasma	miR-142-3p;miR-486-5p;miR-486-3p;miR-130b;miR-532-5p;miR-222;miR-140-5p;miR-122;miR-363;miR-16-1;miR-423-5p miR-221;miR-28-3p;miR-125b;miR-328	+ -
Murri M.	2013	SPAIN	12/12	Blood	miR-21; miR-27b; miR-103	-
Karolina D.S.	2012	AUSTRALIA	32/29	Blood	miR-17;miR-183;miR-197;miR-23a;miR-509-5p;miR-584;miR-652;miR-130a;miR-195;miR-92a;miR-150;miR-192a;miR-27a;miR-320a miR-103	+ -
Pescador N.	2013	SPAIN	20/20	Plasma	miR-15b miR-138 ; miR-376a ; miR-503	+ -
Wang R.	2015	CHINA	123/107	Serum	miR-122	+

Supplementary Table 4: Circulating miRNAs quantification in prediabetic subjects vs controls, revalidated by individual qRT-PCR assays

(+) = increased miRNA concentration in the blood of prediabetic patients compared with controls;

(-) = decreased miRNA concentration in the blood of prediabetic patients compared with controls

References	Years	Countries	Number of prediabetics/controls	Samples	MicroRNAs	Status
PrabuP.	2015	INDIA	47/49	Serum	miR-128 miR-423-5p	+ -
Parrizas M.	2014	SPAIN	24/12	Serum	miR-192; miR-193b; miR-150	+
Liu Y.	2014	CHINA	157/138	Serum	miR-126	-
Karolina D.S.	2011	AUSTRALIA	14/15	Blood	miR-144; miR-192;miR-29a; miR-30d miR-146a; miR-182; miR-150; miR-320a	+ -
Wang Y.T.	2013	TAIWAN	31/71	Serum	miR-221; miR-let7g	+
Zhang T.	2013	CHINA	30/30	Plasma	miR-126	-
Zhao C.	2011	CHINA	24/24	Serum	miR-132; miR-29a; miR-222	-

Supplementary Table 5: Circulating miRNAs quantification in T2DM subjects vs controls, revalidated by individual qRT-PCR assays

(+) = increased miRNA concentration in the blood of diabetic patients compared with controls

(-) = decreased miRNA concentration in the blood of diabetic patients compared with controls

References	Years	Countries	Number of diabetics/controls	Samples	MicroRNAs	Status
Prabu P.	2015	INDIA	49/49	Serum	miR-374a-5p ; miR-130b-3p	+
Higuchi C.	2015	JAPAN	121/83	Serum	miR-101 ; miR-375 ; miR-802	+
Liu Y.	2014	CHINA	160/138	Serum	miR-126	-
Kong L.	2011	CHINA	18/19	Serum	miR-9; miR-29a; miR-30d; miR-34a; miR124a; miR-146a; miR-375	+
Zhang T.	2013	CHINA	30/30	Plasma	miR-126	-
Parrizas M.	2014	SPAIN	10/17	Serum	miR-191; miR-21; miR-139-5p	-
Zampetaki A.	2010	UK	80/80	Plasma	miR-28-3p	+
					miR-15a; miR-20b; miR-21; miR-24; miR-28-3p; miR-29b ; miR-126; miR-150; miR-191; miR-197; miR-223; miR-320; miR-486	-
Karolina D.S.	2011	AUSTRALIA	14/15	Blood	miR-29a; miR-144; miR-150; miR-192; miR-320a miR-30d; miR-146a; miR-182	+
Karolina D.S.	2012	AUSTRALIA	29/29	Blood	miR-27a; miR-150; miR-192; miR-320a	+
					miR-17; miR-92a; miR-130a; miR-197; miR-509-5p; miR-652	-
Wang X.	2014	SWEDEN	33/119	Plasma	miR-15a; miR-21; miR-24; miR-29b; miR-126; miR-150; miR-320a; miR-486-5p	+
Pescador N.	2013	SPAIN	13/20	Serum	miR-503	-
Rong Y.	2013	CHINA	90/90	Plasma	miR-146a	+
Santovito D.	2014	Italie	18/12	Plasma	miR-326	+
				Exosomes	miR-let7a; miR-let7f	-
Ortega F.J.	2014	SPAIN	18 (Obese)/10	Plasma	miR-140-5p; miR-142-3p; miR-222; miR-125b; miR-135b; miR126	+
			30 (Non obese)/35	Plasma	miR-140-5p; miR-142-3p; miR-222; miR-125b; miR-135b; miR-126; miR-423-5p; miR-192; miR-195; miR-532-5p	-

Supplementary Table 6: KEGG pathways significantly enriched in target genes of the 119 human blood miRNAs (Blondal et al. 2013. Methods)
Analyses were performed with DIANA-miRPath (<http://diana.imis.athena-innovation.gr/DianaTools/>)

KEGG PATHWAYS	adjusted p value	number of genes in the pathways	number of blood circulating miRNAs
Pathways in cancer (hsa05200)	3,63E-21	212	77
PI3K-Akt signaling pathway (hsa04151)	7,26E-20	212	76
MAPK signaling pathway (hsa04010)	4,02E-17	172	77
HTLV-I infection (hsa05166)	1,37E-14	144	76
Regulation of actin cytoskeleton (hsa04810)	3,75E-14	135	76
Endocytosis (hsa04144)	4,73E-14	129	73
Focal adhesion (hsa04510)	2,89E-13	131	76
Protein processing in endoplasmic reticulum (hsa04141)	2,82E-12	104	72
Transcriptional misregulation in cancer (hsa05202)	3,12E-12	104	74
Wnt signaling pathway (hsa04310)	5,43E-12	107	77
Chemokine signaling pathway (hsa04062)	3,70E-11	106	75
Calcium signaling pathway (hsa04020)	6,70E-11	100	73
Hepatitis B (hsa05161)	8,71E-11	89	75
Axon guidance (hsa04360)	1,43E-10	88	73
Influenza A (hsa05164)	1,50E-10	97	72
RNA transport (hsa03013)	6,37E-10	91	73
Neurotrophin signaling pathway (hsa04722)	1,77E-09	85	77
Dopaminergic synapse (hsa04728)	1,77E-09	84	75
Ubiquitin mediated proteolysis (hsa04120)	1,77E-09	86	74
Measles (hsa05162)	1,77E-09	82	72
Cell cycle (hsa04110)	1,77E-09	75	71
Oocyte meiosis (hsa04114)	1,82E-09	72	72
Retrograde endocannabinoid signaling (hsa04723)	1,82E-09	70	71
Glutamatergic synapse (hsa04724)	1,96E-09	73	74
Insulin signaling pathway (hsa04910)	3,57E-09	83	75
Jak-STAT signaling pathway (hsa04630)	3,57E-09	83	73
Cholinergic synapse (hsa04725)	3,57E-09	72	71
Vascular smooth muscle contraction (hsa04270)	5,55E-09	71	70
Osteoclast differentiation (hsa04380)	1,96E-08	74	69
Hepatitis C (hsa05160)	1,96E-08	75	66
Serotonergic synapse (hsa04726)	3,09E-08	65	66
TGF-beta signaling pathway (hsa04350)	5,51E-08	61	67
Amoebiasis (hsa05146)	6,05E-08	61	67
Toxoplasmosis (hsa05145)	8,49E-08	65	70
T cell receptor signaling pathway (hsa04660)	9,07E-08	68	72
Glioma (hsa05214)	9,07E-08	46	68
Phosphatidylinositol signaling system (hsa04070)	1,13E-07	54	63
ErbB signaling pathway (hsa04012)	2,26E-07	61	71
Melanogenesis (hsa04916)	2,26E-07	62	69
HIF-1 signaling pathway (hsa04066)	2,76E-07	63	70
Prostate cancer (hsa05215)	2,76E-07	62	69
Chagas disease (American trypanosomiasis) (hsa05142)	4,44E-07	58	69
Tight junction (hsa04530)	5,17E-07	73	74
GnRH signaling pathway (hsa04912)	5,45E-07	60	71
Adherens junction (hsa04520)	6,70E-07	49	72
Small cell lung cancer (hsa05222)	6,70E-07	59	72
Toll-like receptor signaling pathway (hsa04620)	7,44E-07	57	63
Gap junction (hsa04540)	7,78E-07	54	71
Fc gamma R-mediated phagocytosis (hsa04666)	7,78E-07	58	71
Apoptosis (hsa04210)	7,78E-07	55	68
miRNA surveillance pathway (hsa03015)	7,78E-07	55	63
Renal cell carcinoma (hsa05211)	8,49E-07	49	70
Arrhythmic right ventricular cardiomyopathy (ARVC) (hsa05412)	8,49E-07	49	63
Dilated cardiomyopathy (hsa05414)	1,07E-06	56	67
Pancreatic cancer (hsa04974)	1,20E-06	56	61
Pancreatic cancer (hsa05212)	1,33E-06	50	71
Pancreatic secretion (hsa04972)	1,92E-06	50	68
Salivary secretion (hsa04970)	2,43E-06	53	70
Lysine degradation (hsa00310)	2,72E-06	31	67
Long-term depression (hsa04730)	3,04E-06	41	62
Chronic myeloid leukemia (hsa05220)	3,39E-06	49	72
Hypertrophic cardiomyopathy (HCM) (hsa05410)	4,31E-06	50	63
Bacterial invasion of epithelial cells (hsa05100)	4,83E-06	44	67
Progesterone-mediated oocyte maturation (hsa04914)	5,40E-06	50	71
Melanoma (hsa05218)	6,88E-06	47	69
p53 signaling pathway (hsa04115)	7,59E-06	47	71
Gastric acid secretion (hsa04971)	7,59E-06	48	67
Colorectal cancer (hsa05210)	8,51E-06	44	67
mTOR signaling pathway (hsa04150)	1,07E-05	46	70
Long-term potentiation (hsa04720)	1,07E-05	47	67
B cell receptor signaling pathway (hsa04662)	1,37E-05	45	72
Salmonella infection (hsa05132)	1,53E-05	45	67
Inositol phosphate metabolism (hsa00562)	2,24E-05	38	59
Epstein-Barr virus infection (hsa05169)	2,27E-05	106	75
Non-small cell lung cancer (hsa05223)	3,57E-05	36	66
Fc epsilon RI signaling pathway (hsa04664)	3,57E-05	42	64
RNA degradation (hsa03018)	3,57E-05	42	63
Acute myeloid leukemia (hsa05221)	4,02E-05	39	69
Shigellosis (hsa05131)	5,80E-05	37	68
VEGF signaling pathway (hsa04370)	5,80E-05	40	67
Adipocytokine signaling pathway (hsa04920)	8,50E-05	36	64
Endocrine and other factor-regulated calcium reabsorption (hsa04961)	0,000107931	32	58
Viral myocarditis (hsa05416)	0,000107931	37	57
Tuberculosis (hsa05152)	0,000110853	89	73
Endometrial cancer (hsa05213)	0,000120257	36	70
Nicotine addiction (hsa05033)	0,000127111	27	59
Basal cell carcinoma (hsa05217)	0,000153036	35	61
Sphingolipid metabolism (hsa00600)	0,000172706	28	57
Amyotrophic lateral sclerosis (ALS) (hsa05014)	0,000217712	34	63
Epithelial cell signaling in Helicobacter pylori infection (hsa05120)	0,000217712	34	60
Mineral absorption (hsa04978)	0,000217712	34	56
Type II diabetes mellitus (hsa04930)	0,000245918	32	57
Hedgehog signaling pathway (hsa04340)	0,000277848	33	58
N-Glycan biosynthesis (hsa00510)	0,00071666	31	55
Pathogenic Escherichia coli infection (hsa05130)	0,001159342	28	59
ABC transporters (hsa02010)	0,001159342	28	55
Notch signaling pathway (hsa04330)	0,001159342	28	53
Aldosterone-regulated sodium reabsorption (hsa04960)	0,001966793	26	58
Circadian rhythm (hsa04710)	0,002228412	23	53
Bladder cancer (hsa05219)	0,003310688	24	52
Basal transcription factors (hsa03022)	0,004299452	23	48
Thyroid cancer (hsa05216)	0,004876742	19	52
Glycosaminoglycan biosynthesis - keratan sulfate (hsa00533)	0,005532818	11	28
GABAergic synapse (hsa04727)	0,01006108	55	72
Regulation of autophagy (hsa04140)	0,01838983	17	44
Maturity onset diabetes of the young (hsa04950)	0,01838983	15	39
Dorso-ventral axis formation (hsa04320)	0,02089946	17	54
Herpes simplex infection (hsa05168)	0,02206377	92	73
Butanoate metabolism (hsa00650)	0,02353886	16	24
Protein export (hsa03060)	0,03525717	15	28
Cytokine-cytokine receptor interaction (hsa04060)	0,03868065	127	71
Collecting duct acid secretion (hsa04966)	0,04563848	14	24