Exercise Intervention Regulates Fibroblast Growth Factor 21: A Systematic Review and Meta-analysis

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Keywords: Exercise, meta-analysis, fibroblast growth factor 21

Abstract: To clarify the change of fibroblast growth factor 21 (FGF21) concentration in circulating blood induced by exercise intervention in adults, this meta-analysis was designed. PubMed, Medline, and Web of Science databases were searched until July 18, 2022. Two authors work independently, including literature screening, data extraction and quality assessment. RevMan 5.3 and StataSE 15 software were used to data analysis. Eleven studies were eventually included. Compared with the control group, after exercise intervention [SMD = -0.63, 95% CI: -1.17 to -0.08, P = 0.02], the concentration of plasma FGF21 in adults was increased significantly more than control group. Subgroup analysis showed that the effect size was significant in diseased populations [SMD = -1.51, 95% CI: -2.89 to -0.13, P = 0.03]. Regardless of the subjects' BMI, the results showed statistical differences. The effect size was larger in those with $BMI \ge 28$ [SMD = -1.91, 95% CI: -2.91 to -0.91, P = 0.0002] and smaller in those with BMI < 28 [SMD = 0.32, 95% CI: -0.01 to -0.65, P = 0.05]. The promotion of FGF21 concentration by exercise was also correlated with age. When the age of the subjects was equal to and greater than 40 years old, the effect size was significant [SMD = -1.20, 95% CI: -2.13 to -0.26, P = 0.01]. When the duration of exercise intervention was equal to and greater than 40 min, the effect size was significant [SMD = -1.21, 95% CI: -2.18 to -0.25, P = 0.01]. Meta-regression analysis showed that the P value of the subjects' BMI (p = 0.009) was < 0.05, and the subjects' BMI was the main source of heterogeneity. Exercise intervention can increase the concentration of FGF21 in adult plasma, providing a clinical theoretical basis for exercise intervention to regulate FGF21. Currently, there is limited research on exercise intervention, and more research is needed to confirm this theoretical basis due to the complex mechanism of upregulation of FGF21.

1. Introduction

Sports activities and professional sports training have become the foundation of various chronic disease treatments, inducing various forms of exercise adaptations such as increased skeletal muscle blood flow, muscle endurance, and cardiovascular function [1]. Fibroblast growth factor 21 (FGF21), a group of liver-derived proteins, can directly or indirectly affect arterial function by

regulating endothelial dysfunction and inflammatory cell vascular wall infiltration processes [2-4], and is closely related to insulin resistance and prevention of weight gain. Studies have shown that exercise intervention can upregulate FGF21, but there are few studies on the regulation of FGF21 by exercise, and the results are inconsistent [5-8]. FGF21 has potential clinical significance in the treatment of obesity-induced type 2 diabetes and metabolic syndrome. Therefore, whether the overall research results of exercise intervention on FGF21 can support its application in improving chronic diseases is of practical significance. In this study, by collecting articles related to exercise intervention regulating FGF21, we reviewed existing experimental studies and conducted quantitative analysis of the included study results according to the requirements of meta-analysis.

2. Methods

2.1. Source and Retrieval of Studies

Two individuals conducted document retrieval in a double-blind manner using a predetermined search strategy to search databases including PubMed, Web of Science, and Medline. A total of 978 relevant English articles were identified, including 566 from PubMed, 302 from Web of Science, and 110 from Medline. In addition, 2 articles were obtained through reference reading. These 978 articles were imported into Endnote literature management software, and after excluding duplicates, 430 remained. After excluding animal experiments, 132 were obtained. First, articles not relevant to the current meta-analysis were excluded by assessing the title and abstract. After that the text was screened and ultimately 11 articles (17 studies) were included.

2.2. Criteria for the Screening of Studies

2.2.1. Criteria for Inclusion

The inclusion criteria were developed based on the PICOS principle. To maximize the results obtained from the search, the population of interest included individuals of any nationality, gender, and age 18 years or older. And the intervention of interest included any form of physical activity. The study design of interest was randomized controlled trials (RCTs). The measurement of interest was the plasma concentration of FGF21.

2.2.2. Criteria for Exclusion

The exclusion process was conducted independently by researchers (PL and JL). In case of disagreement, a third reviewer determined whether a study met the inclusion criteria. In the process of literature selection, studies with repeated reporting, non-human experiments, non-adult subjects, non-randomized controlled trials, studies that did not measure plasma FGF21 concentrations, studies that used drugs or other means in combination with exercise as an intervention, or studies that did not report exercise regimens in detail were excluded from this meta-analysis.

2.3. Quality Evaluation of Studies

Two authors independently assessed the risk of bias (ROB) according to the Cochrane Collaboration's guidelines in RCT (Figure 1).

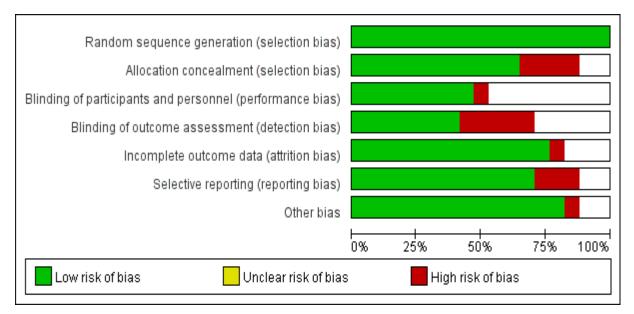


Figure 1: Quality evaluation of included literature.

3. Data Extraction and Statistical Analysis

RevMan 5.3 software was used for pooled effect size and subgroup analysis, and meta-regression analysis was performed on the data using Stata-SE15.1 software. The effect size indicators for continuous variable outcome measures were described as weighted mean differences (WMD) or standardized mean differences (SMD), and the corresponding 95% confidence intervals (CI) were calculated. According to the Cochrane Handbook, the choice between WMD and SMD depended on the similarity or difference of the outcome measure evaluation criteria. The heterogeneity was tested by Q-test and I2-test. When P \geq 0.05 and I2 \leq 50%, a fixed-effect model was used for meta-analysis. While P < 0.05 and I2 > 50%, a random effect model was used for meta-analysis failed to explain the source of heterogeneity, meta-regression was used. Getdata2.20 software was used to extract the mean values and standard deviations from the histogram for studies that only provided outcome measure data. The data extraction included basic information of the studies, research type and methodological characteristics, characteristics of the study population, intervention measures, sample size, and other relevant indicators (Table 1).

4. Results

4.1. Results of Meta-analysis

4.1.1. Regulation of FGF21 by Exercise Intervention

The 11 included studies (17 interventions) were combined, and as shown in Figure 2, the heterogeneity test was I2 = 87% and P < 0.00001. It indicates that there is significant heterogeneity across studies. Therefore, a random effects model was used in present meta-analysis. The pooled effect size was [SMD = -0.63, 95%CI: -1.17 to -0.08, P = 0.02], indicating a significant difference. Exercise intervention significantly increased FGF21 concentration in the plasma of adults compared with the control group. Therefore, exercise intervention can significantly improve plasma FGF21 concentration in adults.

Author and year	Sample size	Study population	Gender	BMI	Age	Intervention cycle	Intervention duration
Asghar 2021 [9]	10	Healthy	Female	31 ± 2	30 ± 3	8	47min
Saeidi 2019 [10]	12	Healthy	Female	28 ± 2	56 ± 5	8	48min
Banitalebi-A 2019 [11]	17	T2D	-	33 ± 6	55 ± 6	10	20min
Banitalebi-B 2019 [11]	17	T2D	-	34 ± 5	54 ± 5	10	40min
Ghanbari-A 2018 [12]	17	Healthy	Male	22 ± 2	23 ± 2	Acute	45-50
Ghanbari-B 2018 [12]	17	Healthy	Male	22 ± 2	23 ± 2	Acute	45-50
Ghanbari-C 2018 [12]	17	Healthy	Male	22 ± 2	23 ± 2	Acute	50
Kozlowska 2021 [13]	27	Healthy	-	32 ± 3	42 ± 13	2	25min
Sanayei 2022 [14]	11	Healthy	Female	-	25 ± 3	8	25-30min
Scharhag 2018 [15]	10	Healthy	Male	-	-	Acute	1h
Farzanegi-A 2022 [16]	14	T2D	Female	32 ± 3	51 ±7	8	40min
Farzanegi-B 2022 [16]	14	T2D	Female	30 ± 4	53 ± 1	8	40min
Scalzo 2014 [17]	19	Healthy	Male	28 ± 1	24 ± 1	3	-
Shabkhiz 2021 [18]	12	Healthy	Female	28 ± 4	72 ± 5	12	-
Shabani 2020 [19]	23	NAFLD	8 male/15 Female	28 ±4	56 ±12	12	20-30min
Kong-A 2016 [20]	10	Healthy	Male	34 ± 6	20 ± 1	5	20min
Kong-B 2016 [20]	8	Healthy	Male	34 ±4	20 ± 2	5	40min

Table 1: Baseline characteristics of participants.

	Exp	perimental		0	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Asghar Tofighi2017	250.85	4.44	10	265.93	6.62	10	5.1%	-2.56 [-3.81, -1.32]	
Ayoub Saeidi2019	254.6	13.258	12	281.6	5.5	12	5.3%	-2.57 [-3.70, -1.44]	
Ebrahim Banitalebi-A2018	170.11	71.02	17	229.63	94.89	17	6.2%	-0.69 [-1.39, 0.00]	
Ebrahim Banitalebi-B2018	176.31	94.22	17	204.67	111.36	17	6.3%	-0.27 [-0.94, 0.41]	-+
HE Z-A2018	65.714	59.831	17	36.078	25.937	17	6.3%	0.63 [-0.06, 1.32]	<u> </u>
HE Z-B2018	61.006	59.7577	17	36.966	35.121	17	6.3%	0.48 [-0.20, 1.16]	+
HE Z-C2018	66.241	82.295	17	34.407	42.948	17	6.3%	0.47 [-0.21, 1.16]	+
Koz# P wska-Flis2021	191	91.8	27	275	178.8	27	6.5%	-0.58 [-1.13, -0.04]	
Mahzad Sanayei2022	950.31	1,001.45	11	692.32	680.94	11	6.0%	0.29 [-0.55, 1.13]	+-
Morville2018	46	11	10	74	20	10	5.5%	-1.66 [-2.71, -0.61]	
P Farzanegi-A2022	267.57	28.62	14	393.43	33.39	14	4.9%	-3.93 [-5.26, -2.59]	_ - _
P Farzanegi-B2022	289	21.41	14	364.71	19.55	14	5.1%	-3.59 [-4.84, -2.33]	
scalzo 2014	338	339.99	19	251	156.92	19	6.3%	0.32 [-0.32, 0.96]	+
Shabkhiz, Fatemeh2020	336.14	95.43	12	253.24	116.13	12	6.0%	0.75 [-0.08, 1.59]	
Takahashi, Atsushi2020	184.6	113.3	23	142.9	105.9	23	6.4%	0.37 [-0.21, 0.96]	+
Zhaowei Kong-A2016	0.5	0.4	10	0.5	0.4	10	5.9%	0.00 [-0.88, 0.88]	_
Zhaowei Kong-B2016	0.6	0.7	8	0.6	0.6	8	5.7%	0.00 [-0.98, 0.98]	+
Total (95% CI)			255			255	100.0%	-0.63 [-1.17, -0.08]	•
Heterogeneity: Tau ² = 1.10; C	⊳hi² = 125	.79. df = 16	6 (P < 0	.00001):	I² = 87%				
Test for overall effect: Z = 2.2								-	-4 -2 0 2 4
		_,						F:	avours experimental Favours control

Figure 2: Meta-analysis forest map of plasma FGF21 concentration regulated by exercise.

	Corf.	Std. Err.	t	Р	95%	CI
Study population	1.199	0.737	1.63	0.179	-0.846	3.244
BMI	3.139	0.659	-4.76	0.009	-4.967	-1.31
Age	-0.152	0.852	-0.02	0.987	-2.382	2.351
Intervention duration	-0.463	0.485	-0.96	0.394	-1.809	0.883

Table 2: Results of meta-regression analysis.

When the number of included studies exceeds 10 and the heterogeneity I2 is greater than 50%, regression analysis is needed to further explore the potential sources of heterogeneity. In this study, four covariates were set according to the extracted data from the literature, including age of the participants, BMI of the participants, population of the participants, and intervention duration for exercise intervention. Meta-regression analysis (see Table 2) showed that the P value of the subjects' BMI (p = 0.009) was less than 0.05, while the P values of the subjects' population (p = 0.179), age (p = 0.987), and intervention duration (p = 0.394) were greater than 0.05. Therefore, the subjects' BMI was the main source of heterogeneity, while the subjects' age, population, and intervention duration may also be sources of heterogeneity.

4.1.2. Subgroup Analysis of Regulation of Exercise on FGF21

2.1.1 Healthy population	Exp Mean	erimental SD	Total		Control SD	Total	Weight	Std. Mean Difference IV. Random, 95% Cl	Std. Mean Difference IV. Random, 95% CI
Asghar Tofighi2017	250.85	4.44	10	265.93	6.62	10	1.5%	-2.56 [-3.81, -1.32]	
Ayoub Saeidi2019	254.6	13.258	12	281.6	5.5	12	1.5%	-2.57 [-3.70, -1.44]	<u> </u>
HE Z-A2018	65.714	59.831	17	36.078		17	1.8%	0.63 [-0.06, 1.32]	-
HE Z-B2018	61.006	59.7577	17	36.966	35.121	17	1.8%	0.48 [-0.20, 1.16]	
HE Z-C2018	66.241 191	82.295 91.8	17 27	34.407 275	42.948 178.8	17 27	1.8% 1.9%	0.47 [-0.21, 1.16]	
Koz† P wska-Flis2021 Mahzad Sanayei2022		91.8 1,001.45	11	692.32	680.94	27	1.9%	-0.58 [-1.13, -0.04] 0.29 [-0.55, 1.13]	
scalzo 2014	338	339.99	19	251	156.92	19	1.8%	0.32 [-0.32, 0.96]	+
Shabkhiz, Fatemeh2020	336.14	95.43	12	253.24	116.13	12	1.7%	0.75 [-0.08, 1.59]	
Zhaowei Kong-A2016	0.5	0.4	10	0.5	0.4	10	1.7%	0.00 [+0.88, 0.88]	
Zhaowei Kong-B2016	0.6	0.7	8 160	0.6	0.6	8 160	1.6% 18.9%	0.00 [-0.98, 0.98]	—
Subtotal (95% CI) Heterogeneity: Tau ² = 0.65; (Chi2 = 52	01 df = 10		00001)-	12 = 81%		18.9%	-0.16 [-0.70, 0.38]	•
Test for overall effect: Z = 0.5			(,		1 - 01%				
2.1.2 Disease population Ebrahim Banitalebi-A2018	170.11	71.02		229.63	94.89	17	1.8%	-0.69 [-1.39, 0.00]	
Ebrahim Banitalebi-A2018 Ebrahim Banitalebi-B2018	170.11	94.22	17 17	229.63		17	1.8%	-0.69 [-1.39, 0.00] -0.27 [-0.94, 0.41]	
P Farzanegi-A2022	267.57	28.62	14	393.43	33.39	14	1.4%	-3.93 [-5.26, -2.59]	
P Farzanegi-B2022	289	21.41	14	364.71	19.55	14	1.5%	-3.59 [-4.84, -2.33]	
Takahashi, Atsushi2020	184.6	113.3	23	142.9	105.9	23	1.9%	0.37 [-0.21, 0.96]	
Subtotal (95% CI)	0.12 - 67	07 45 - 44	85	000041-1	2 - 020/	85	8.3%	-1.51 [-2.89, -0.13]	
Heterogeneity: Tau ² = 2.24; 0 Test for overall effect: Z = 2.1	15 (P = 0.)	27, df = 4 (03)	P < 0.	30001); 1	× = 93%				
2.1.3 BMI ≥ 28									
Asghar Tofighi2017	250.85	4.44		265.93	6.62	10	1.5%	-2.56 [-3.81, -1.32]	<u> </u>
Ayoub Saeidi2019	254.6	13.258	12	281.6	5.5	12	1.5%	-2.57 [-3.70, -1.44]	
Ebrahim Banitalebi-A2018 Ebrahim Banitalebi-B2018	170.11 176.31	71.02 94.22	17 17	229.63 204.67	94.89 111.36	17 17	1.8% 1.8%	-0.69 [-1.39, 0.00] -0.27 [-0.94, 0.41]	
Ebrahim Banitalebi-B2018 Koz† P wska-Flis2021	176.31	94.22 91.8	17 27	204.67	111.36 178.8	17 27	1.8% 1.9%	-0.27 [-0.94, 0.41] -0.58 [-1.13, -0.04]	
P Farzanegi-A2022	267.57	28.62	14	393.43	33.39	14	1.4%	-3.93 [-5.26, -2.59]	<u> </u>
P Farzanegi-B2022	289	21.41	14	364.71	19.55	14	1.5%	-3.59 [-4.84, -2.33]	
Subtotal (95% CI)			111			111	11.4%	-1.91 [-2.91, -0.91]	➡
Heterogeneity: Tau ² = 1.56; 0 Test for overall effect: Z = 3.3	Chi ² = 54. 75 (P = 0.)	45, df = 6 (0002)	P < 0.	30001); I	* = 89%				
2.1.4 BMI < 28									
HE Z-A2018	65.714	59.831	17	36.078		0		Not estimable	
HE Z-B2018	61.006	59.7577	17	36.966	35.121	0		Not estimable	ļ
HE Z-C2018	66.241	82.295	17	34.407	42.948	0	4.00.	Not estimable	<u>+</u>
scalzo 2014 Shabkhiz, Fatemeh2020	338 336.14	339.99 95.43	19 12	251 253.24	156.92 116.13	19 12	1.8% 1.7%	0.32 [-0.32, 0.96] 0.75 [-0.08, 1.59]	—
Takahashi, Atsushi2020	330.14	95.43	23	253.24	105.9	23	1.7%	0.37 [-0.21, 0.96]	+
Zhaowei Kong-A2016	0.5	0.4	10	0.5	0.4	10	1.7%	0.00 [-0.88, 0.88]	+
Zhaowei Kong-B2016	0.6	0.7	8	0.6	0.6	8	1.6%	0.00 [-0.98, 0.98]	-
Subtotal (95% CI)	0.00	0 46 - 1 -	123	43-12-01	07	72	8.8%	0.32 [-0.01, 0.65]	
Heterogeneity: Tau ² = 0.00; 0 Test for overall effect: Z = 1.9			= 0.7	ŧ); I ^x = Ο	70				
2.1.5 Age ≽ 40									
Ayoub Saeidi2019	254.6	13.258	12	281.6	5.5	12	1.5%	-2.57 [-3.70, -1.44]	
Ebrahim Banitalebi-A2018	170.11	71.02	17	229.63	94.89	17	1.8%	-0.69 [-1.39, 0.00]	
Ebrahim Banitalebi-B2018	176.31	94.22	17	204.67		17	1.8%	-0.27 [-0.94, 0.41]	
Koz† P wska-Flis2021 P Farzanegi-A2022	191 267.57	91.8 28.62	27 14	275 393.43	178.8 33.39	27 14	1.9% 1.4%	-0.58 [-1.13, -0.04] -3.93 [-5.26, -2.59]	
P Farzanegi-B2022	289	21.41	14	364.71	19.55	14	1.5%	-3.59 [-4.84, -2.33]	<u> </u>
Shabkhiz, Fatemeh2020	336.14	95.43	12	253.24	116.13	12	1.7%	0.75 [-0.08, 1.59]	
Takahashi, Atsushi2020	184.6	113.3	23	142.9	105.9	23	1.9%	0.37 [-0.21, 0.96]	▲ ^{†−}
Subtotal (95% CI) Heterogeneity: Tau ² = 1.61; (136 P < 0.	00001); I	² = 91%	136	13.5%	-1.20 [-2.13, -0.26]	▼
Test for overall effect: Z = 2.0	51 (P = 0.)					10	4 50		
Test for overall effect: Z = 2.8									
2.1.6 Age <40 Asghar Tofighi2017	250.85	4.44		265.93	6.62		1.5%	-2.56 [-3.81, -1.32]	
2.1.6 Age ≪40 Asghar Tofighi2017 HE Z-A2018	250.85 65.714	59.831	17	36.078	25.937	17	1.8%	0.63 [-0.06, 1.32]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-B2018	250.85							0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-B2018 HE Z-C2018 Mahzad Sanayei2022	250.85 65.714 61.006 66.241 950.31	59.831 59.7577 82.295 1,001.45	17 17 17 11	36.078 36.966 34.407 692.32	25.937 35.121 42.948 680.94	17 17 17 11	1.8% 1.8% 1.8% 1.7%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-B2018 Mahzad Sanayei2022 scalzo 2014	250.85 65.714 61.006 66.241 950.31 338	59.831 59.7577 82.295 1,001.45 339.99	17 17 17 11 19	36.078 36.966 34.407 692.32 251	25.937 35.121 42.948 680.94 156.92	17 17 17 11 19	1.8% 1.8% 1.8% 1.7% 1.8%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-2018 Hahzad Sanayei2022 scalzo 2014 Zhaowei Kong-A2016	250.85 65.714 61.006 66.241 950.31 338 0.5	59.831 59.7577 82.295 1,001.45 339.99 0.4	17 17 17 11 19 10	36.078 36.966 34.407 692.32 251 0.5	25.937 35.121 42.948 680.94 156.92 0.4	17 17 17 11 19 10	1.8% 1.8% 1.7% 1.8% 1.7%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.88, 0.88]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-B2018 HE Z-C2018 Mahzad Sanayei2022 scalzo 2014 Zhaowei Kong-A2016 Zhaowei Kong-B2016	250.85 65.714 61.006 66.241 950.31 338	59.831 59.7577 82.295 1,001.45 339.99	17 17 17 11 19	36.078 36.966 34.407 692.32 251	25.937 35.121 42.948 680.94 156.92	17 17 17 11 19	1.8% 1.8% 1.8% 1.7% 1.8% 1.7% 1.6%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.32 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.88, 0.88] 0.00 [-0.98, 0.98]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-C2018 Mahzad Sanayei2022 scalzo 2014 Zhaowei Kong-A2016 Zhaowei Kong-B2016 Subtotal (85% CI) Subtotal (85% CI)	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi ² = 22.	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (17 17 11 19 10 8 109	36.078 36.966 34.407 692.32 251 0.5 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6	17 17 11 19 10 8	1.8% 1.8% 1.7% 1.8% 1.7%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.88, 0.88]	
2.1.6 Age <40 Asphar Tofshi2017 HE Z-42018 HE Z-42018 HE Z-42018 Mahzad Sanaye/2022 scalzo 2014 Zhaowei Kong-82016 Zhaowei Kong-82016 Zhaowei Kong-82016 Zhaowei Kong-7016 Zhaowei Kong-7016 Zhaowei Kong-82016 Subtofat (95% C1) Feet for overall effect: Z = 0.35;	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi ² = 22. 31 (P = 0.	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76)	17 17 11 19 10 8 109	36.078 36.966 34.407 692.32 251 0.5 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6	17 17 11 19 10 8	1.8% 1.8% 1.8% 1.7% 1.8% 1.7% 1.6%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.32 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.88, 0.88] 0.00 [-0.98, 0.98]	
2.1.6 Age <40 Asphar Tofiphi2017 HE Z-A2018 HE Z-B2018 HE Z-C2018 Mahzad Sanayei2022 Sanavei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Satotatai (9%-C 0.35; Katotatai (9%-C 0.35; Test for versai feret; Z = 0.3	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76)	17 17 17 19 10 8 109 P = 0.	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² =	25.937 35.121 42.948 680.94 156.92 0.4 0.6	17 17 11 19 10 8 109	1.8% 1.8% 1.7% 1.8% 1.7% 1.6% 13.8%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.88, 0.88] 0.00 [-0.88, 0.98] 0.08 [-0.42, 0.58]	
2.1.6 Age <40 Asghar Tofighi2017 HE Z-A2018 HE Z-2018 Hahzad Sanayei2022 scalzo 2014 Zhaowei Kong-A2016	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi ² = 22. 31 (P = 0.	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76)	17 17 17 19 10 8 109 P = 0.	36.078 36.966 34.407 692.32 251 0.5 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6	17 17 11 19 10 8	1.8% 1.8% 1.8% 1.7% 1.8% 1.7% 1.6%	0.63 [0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.29 [-0.35, 1.13] 0.20 [-0.32, 0.96] 0.00 [-0.88, 0.88] 0.00 [-0.48, 0.98] 0.08 [-0.42, 0.58]	
2.1.6 Age <40 Asghar Tofshi2017 HE Z-A2018 HE Z-A2018 HE Z-C2018 Sanayei2022 Zinaowei Kong-A2016 Zinaowei Kong-A2016 Zinaowei Kong-A2016 Subtotal (95% CI) Heterogeneity: Tau ² = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Asghar Tofshi2017	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min 250.85	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22	17 17 11 19 10 8 109 P = 0.1	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 111.36	17 17 11 19 10 8 109	1.8% 1.8% 1.7% 1.8% 1.7% 1.6% 13.8%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.29 [-0.55, 1.13] 0.29 [-0.58, 0.88] 0.00 [-0.98, 0.98] 0.08 [-0.42, 0.56] -2.56 [-3.81, -1.32] -2.57 [-3.70, -1.44] -0.27 [-0.94, 0.41]	
2.1.6 Age ~40 Asphar Tofphi2017 HE 2-A2016 HE 2-A2018 HE 2-C2018 HE 2-C2018 Ananzad Sanayei2022 Sanayei2022 Sanayei2022 Sanayei2022 Haterzoganaky: Tau" = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Asphar Tofphi2017 Ayoub Saeid2019 Ebrahim Banitalebi-B2018 HE 2-A2018	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min 250.85 254.6 176.31 65.714	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.831	17 17 17 19 10 8 109 P = 0 10 12 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 111.36 25.937	17 17 11 19 10 8 109 10 12 17 17	1.8% 1.8% 1.7% 1.8% 1.6% 1.6% 13.8% 1.5% 1.5% 1.8%	$\begin{array}{c} 0.63 & [0.06, 1.32] \\ 0.48 & [-0.20, 1.16] \\ 0.47 & [-0.21, 1.16] \\ 0.29 & [-0.55, 1.13] \\ 0.32 & [-0.32, 0.36] \\ 0.00 & [-0.88, 0.88] \\ 0.00 & [-0.88, 0.88] \\ 0.08 & [-0.42, 0.58] \\ \hline \\ \begin{array}{c} -2.56 & [-3.81, -1.32] \\ -2.57 & [-3.70, -1.44] \\ -0.27 & [-0.34, 0.41] \\ 0.63 & [-0.06, 1.32] \\ \end{array}$	
2.1.6 Age <40 Asghar Tofshi2017 HE Z-A2018 HE Z-A2018 HE Z-C2018 Sanayei2022 Sanayei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Heterogeneity: Tau ² = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Asghar Tofshi2017 Ayoub Sacid2019 Exhain Bacid2019 Exhain Bacid2019 HE Z-A2018 HE Z-A2018	250.85 65.714 61.006 66.241 950.31 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min 250.85 254.6 176.31 65.714 61.006	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 12, df = 7 (76) 14.44 13.258 94.22 59.831	17 17 11 19 10 8 109 P = 0 10 12 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078 36.966	25.937 35.121 42.948 680.94 156.92 0.4 0.6 6.62 5.5 111.36 25.937 35.121	17 17 11 19 10 8 109 10 12 17 17 17	1.8% 1.8% 1.7% 1.6% 1.6% 13.8% 1.5% 1.8% 1.8%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.98, 0.98] 0.08 [-0.42, 0.58] 0.08 [-0.42, 0.58] -2.56 [-3.81, -1.32] -2.57 [-3.70, -1.44] 0.27 [-0.94, 0.41] 0.35 [-0.06, 1.32] 0.48 [-0.02, 1.16]	
2.1.6 Age <40 Asphar Tofphi2017 HE Z-A2018 HE Z-A2018 HE Z-B2018 HE Z-C2018 Zhaowei Kong-A2016 Zhaowei Kong-A2016 HE Z-A2018 HE Z-A2018	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0.² ≥ 40min 250.85 254.6 176.31 65.714 61.006 66.241	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.8577 82.295	17 17 11 19 10 8 109 P = 0 10 12 17 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.966 34.407	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 111.36 25.937 35.121 42.948	17 17 11 19 10 8 109 10 12 17 17 17 17	1.8% 1.8% 1.7% 1.6% 1.6% 1.5% 1.5% 1.8% 1.8% 1.8% 1.8%	$\begin{array}{c} 0.63 \ [0.06, 1.32] \\ 0.45 \ [0.20, 1.16] \\ 0.47 \ [0.22, 1.16] \\ 0.27 \ [0.55, 1.13] \\ 0.32 \ [0.35, 1.33] \\ 0.32 \ [0.35, 0.86] \\ 0.00 \ [0.86, 0.88] \\ 0.00 \ [0.98, 0.88] \\$	
2.1.6 Age <40 Asghar Tofshi2017 HE Z-A2018 HE Z-A2018 HE Z-C2018 Sanayei2022 Sanayei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Heterogeneity: Tau ² = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Asghar Tofshi2017 Ayoub Sacid2019 Exhain Bacid2019 Exhain Bacid2019 HE Z-A2018 HE Z-A2018	250.85 65.714 61.006 66.241 950.31 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min 250.85 254.6 176.31 65.714 61.006	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 12, df = 7 (76) 14.44 13.258 94.22 59.831	17 17 11 19 10 8 109 P = 0 10 12 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078 36.966	25.937 35.121 42.948 680.94 156.92 0.4 0.6 6.62 5.5 111.36 25.937 35.121	17 17 11 19 10 8 109 10 12 17 17 17	1.8% 1.8% 1.7% 1.6% 1.6% 13.8% 1.5% 1.8% 1.8%	0.63 [-0.06, 1.32] 0.48 [-0.20, 1.16] 0.47 [-0.21, 1.16] 0.29 [-0.55, 1.13] 0.32 [-0.32, 0.96] 0.00 [-0.86, 0.88] 0.00 [-0.96, 0.98] 0.08 [-0.42, 0.58] -2.56 [-3.81, -1.32] -2.57 [-3.70, -1.44] 0.27 [-0.94, 0.41] 0.35 [-0.06, 1.32] 0.48 [-0.20, 1.16]	
2.1.6 Age <40 Asghar Tofshi2017 HE Z-A2018 HE Z-A2018 HE Z-20218 Sanayei2022 Sanayei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Heterogeneity: Tau ² = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Asghar Tofshi2017 Ayoub Saeidi2019 HE Z-A2018 HE Z-A2018 HE Z-2018 Moville2018 P Farzanegi-A2022	250.85 65.714 61.064 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0.) ≥ 40min 250.85 254.6 176.31 65.714 61.06 66.241 46 267.57 289	59.831 59.777 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.8577 82.295 11 28.62 21.41	17 17 17 11 19 10 8 109 P = 0. 10 12 17 17 17 17 17 17 17 10 14 14	36.078 36.966 34.407 692.32 251 0.5 0.6 002); l ² = 265.93 281.6 204.67 36.078 36.966 34.407 74 393.43 364.71	25.937 35.121 42.948 680.94 156.92 0.4 0.6 6.62 5.5 111.36 25.937 35.121 42.948 20 33.39 19.55	17 17 11 19 10 8 109 10 12 17 17 17 17 17 14 14	1.8% 1.8% 1.7% 1.6% 1.6% 1.5% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.27 \\ 0.47 \\ 0.$	
2.1.6 Age ~40 Asphar Tofphi2017 HE Z-A2018 HE Z-A2018 HE Z-B2018 HE Z-B2018 HE Z-C2018 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Her Z-B2018 HE Z-B2018 HE Z-A2018 Morvilac2018 P Farzanegi-A2022 P Farzanegi-A2012 P Farzanegi-A2012 P Farzanegi-A2012	250.85 65.714 61.006 66.241 338 0.5 0.6 Chi² = 22. 31 (P = 0. ≥ 40min 250.85 254.6 176.31 65.714 61.006 66.241 46 267.57	59.831 59.777 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.831 59.7577 82.295 111 28.62	17 17 17 11 19 10 8 109 P = 0. 10 12 17 17 17 17 17 17 17 10 14 14 8	36.078 36.966 34.407 692.251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078 36.966 34.407 74 393.43	25.937 35.121 42.948 680.94 156.92 0.4 0.6 668% 6.62 5.5 111.36 25.937 35.121 42.948 20 33.39	17 17 19 10 8 109 10 127 17 17 17 17 10 14 8	1.8% 1.8% 1.7% 1.8% 1.6% 1.6% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.6%	$\begin{array}{c} 0.85 \\ 0.85 \\ 0.48 \\ 1.02 \\ 0.28 \\ 1.02 \\ 0.48 \\ 1.02 \\ 1.02 \\ 0.00 \\ 1.02 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.$	
2.1.6 Age <40 Asphar Tofphi2017 HE Z-A2018 HE Z-A2018 HE Z-B2018 HE Z-B2018 Sanayei2022 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Subtotal (95% CI) Subtotal (95% CI) Z-1.7 Intervention duration Asphar Tofphi2017 Ayoub Sanid2019 Ebrahim Banitalebi-82018 HE Z-A2018 HE Z-A2018 Morville2018 P Farzanegi-A2022	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi² = 22. 31 (P = 0. ≥ 40min 250.85 254.6 176.31 65.714 61.006 66.241 41.006 66.241 65.757 289 0.6	59.831 59.777 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.831 59.7577 82.295 111 28.62 21.41 0.7	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 10 14 14 8 136	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078 36.966 34.407 74 393.43 364.71 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 5111.36 25.937 35.121 42.948 20 33.39 19.55 0.6	17 17 11 19 10 8 109 10 12 17 17 17 17 17 14 14	1.8% 1.8% 1.7% 1.6% 1.6% 1.5% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.27 \\ 0.47 \\ 0.$	
2.1.6 Age <40 Asghar Tofph2017 HE Z-A2018 HE Z-A2018 HE Z-32018 HE Z-32018 LE Z-32018 Sanayei2022 Zinaowei Kong-A2016 Zinaowei Kong-A2016 Zinaowei Kong-B2016 Subtotal (95% CI) Asghar Tofph2017 Ayoub Saedi2019 HE Z-42018 HE Z-42018	250.85 65.714 61.006 66.241 950.31 338 0.5 0.6 Chi ² = 22. 33 (P = 0. ≥ 40min 250.85 254.6 176.31 65.714 61.006 66.241 9.06 Chi ² = 104 Chi ² =	59.831 59.777 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 12, df = 7 (76) 13.258 94.22 59.831 59.7577 82.295 11 28.62 21.41 0.7	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 10 14 14 8 136	36.078 36.966 34.407 692.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.078 36.966 34.407 74 393.43 364.71 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 5111.36 25.937 35.121 42.948 20 33.39 19.55 0.6	17 17 19 10 8 109 10 127 17 17 17 17 10 14 8	1.8% 1.8% 1.7% 1.8% 1.6% 1.6% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.6%	$\begin{array}{c} 0.85 \\ 0.85 \\ 0.48 \\ 1.02 \\ 0.28 \\ 1.02 \\ 0.48 \\ 1.02 \\ 1.02 \\ 0.00 \\ 1.02 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.00 \\ 1.00 \\ 0.$	
2.1.6 Age ~40 Asphar Toffpi2017 HE Z-A2016 HE Z-A2018 HE Z-A2018 HE Z-A2018 HE Z-C2018 Ananza Sannye/2022 Sannye/2	250.85 65.714 61.006 66.241 950.31 950.31 (P = 0. ≥ 40min 250.85 254.6 176.31 65.714 61.006 66.241 46 267.57 289 0.6 Chi ² = 104 47 (P = 0.) < < 40min	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 12, df = 7 (76) 14, 444 13.258 94.22 59.831 59.7577 82.295 111 28.62 21.41 0.7	17 17 17 19 10 8 109 P = 0. 10 12 17 17 17 17 17 17 17 10 14 8 136 (P < 0	36.078 36.966 692.32 251 0.5 0.6 0002); I ² = 265.93 281.6 204.67 36.078 36.966 34.407 734.3 364.71 0.6	25.937 35.121 42.948 680.94 156.92 0.4 0.6 68% 6.62 5.5 111.36 25.937 35.121 42.948 20 33.39 19.555 0.6	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 10 14 14 8 136	1.8% 1.8% 1.7% 1.6% 1.6% 1.5% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.6%	$\begin{array}{c} 0.85 \\ 0.85 \\ 0.48 \\ (-20, -1.66 \\ 0.47 \\ (-22, -1.66 \\ 0.28 \\ (-25, -1.33 \\ 0.32 \\ (-25, -1.33 \\ 0.32 \\ (-25, -1.33 \\ 0.33 \\ (-$	
2.1.6 Age <40 Asphar Tofphi2017 HE Z-A2016 HE Z-A2018 HE Z-B2018 HE Z-B2018 HE Z-C2018 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Hearogenetix, Tau" = 0.35; Tast for overall effect 2 = 0. Z-1.7 Intervention duration Asphar Tofghi2017 Pauba Boalebi-B2018 HE Z-B2018 HE Z-B2018 HE Z-B2018 HE Z-B2018 Morville2018 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2012 Subtotal (95% CI) Test for overall effect: Z = 2. 2.1.8 Intervention duration	$\begin{array}{c} 250.85\\ 65.714\\ 950.31\\ 950.31\\ 950.31\\ 950.33\\ 0.6\\ 66.241\\ 950.33\\ 0.6\\ 66.241\\ 250.85\\ 254.6\\ 61.006\\ 66.241\\ 46\\ 61.006\\ 66.241\\ 46\\ 66.241\\ 26.75\\ 29.9\\ 0.6\\ Chi^2=10\\ 47(P=0)\\ 0.6\\ Chi^2=10\\ 47(P=0)\\ 176.31\\ 1$	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.831 59.7577 82.295 11 28.62 21.41 0.7 4.09, df = 9 01) 94.22	17 17 17 19 10 10 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	36.078 36.966 36.966 052.32 251 0.5 0.6 002); I ² = 265.93 281.6 204.67 36.976 34.407 74 393.43 364.71 0.6 0.00001); 204.67	25.937 35.121 42.948 680.94 156.92 0.4 0.6 6.62 5.5 3. 35.121 111.36 25.937 35.121 111.36 25.937 35.121 111.36	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 14 4 8 136	1.8% 1.8% 1.7% 1.6% 1.6% 1.5% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.4% 1.5% 1.6% 16.3%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.016 \\ 1.68 \\ 0.001 \\ 0.48 \\ 0.001 \\ $	
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2.1.6 Age <40 Asphar Tofphi2017 HE Z-A2016 HE Z-A2018 HE Z-A2018 HE Z-A2018 Sanayei2022 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) 44erosgenetiz, Tau' = 0.35; Test for overall effect: 2 = 0.32; Z.1.7 Intervention duration Asphar Tofphi2017 Vyoub Saedi2019 Exclamb Bantalesi-B2018 Charlos Bantalesi-B2018 HE Z-B2018 HE Z-C2016 Morville2018 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 Z.1.8 Intervention duration duration duration Subtotal (95% CI) Test for overall effect: Z = 2 2.1.8 Intervention duration Mazad Sanaye2022	250.85 65.714 65.714 66.241 338 0.5 0.6 Chi ² = 22. 250.85 250.85 250.85 250.85 267.57 289 0.6 Chi ² = 104 Chi ² = 104 Ch	59.831 59.7577 82.295 339.99 0.4 0.7 12, df = 7 (76) 4.44 13.258 94.22 59.831 59.7577 82.295 11 28.62 21.41 0.7 4.09, df = 9 01) 94.22 91.8 1.001.45	17 17 17 19 10 10 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	36.078 36.966 36.967 692.32 251 0.5 0.6 0002); I ² = 265.93 281.6 204.67 36.078 36.978 36.407 74 393.43 364.71 0.6 204.67 7275	25337 35.121 42.948 680.94 156.92 0.4 0.6 68% 68% 68% 68% 20 33.39 19.55 20 33.39 19.55 20 33.39 19.55 20 33.39 19.55 20 33.91 111.36 680.94	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 14 4 8 136	1.8% 1.8% 1.7% 1.7% 1.6% 1.5% 1.5% 1.3% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.6%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116 \\ 0.28 \\ 1.65 \\ 0.116$	
2.1.6 Age <40 Asphar Tofphi2017 HE Z-A2018 HE Z-A2018 HE Z-A2018 HE Z-A2018 HE Z-C2018 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Zhaowei Kong-A2016 Subtotal (95% CI) Asphar Tofphi2017 Nyoub Saedi2019 HE Z-A2018 HE Z-A2018 H	250.85 65.714 950.31 338 0.5 Chi ² = 22. 31 (P = 0. 254.6 66.241 176.31 65.714 261.006 66.241 261.006 66.241 261.006 66.241 261.006 66.241 27. 289 0.6 Chi ² = 104 267.57 289 0.6 Chi ² = 104 267.57 289 0.6 Chi ² = 104 267.57 289 0.6 Chi ² = 2.2 254.6 Chi ² = 2.2 Chi ² = 104 Chi	59.831 59.7577 82.295 1,001.45 339.99 0.4 0.7 12, df = 7 (76) 94.22 59.831 59.7577 82.295 111 28.62 21.41 0.7 4.09, df = 9 01) 94.22 91.8	17 17 17 11 19 10 8 109 P = 0. 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	36.078 36.966 (34.407 692.32 2511 0.5 0.6 002): I ² = 265.93 281.6 281.6 281.6 36.968 36.966 34.407 74 393.43 34.407 74 393.43 364.71 0.6 0.00001): 204.67 275 5692.32	25337 35.121 42.948 680.94 156.92 0.4 0.6 68% 68% 68% 68% 20 33.39 19.55 20 33.39 19.55 20 33.39 19.55 20 33.39 19.55 20 33.91 111.36 680.94	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	1.8% 1.8% 1.7% 1.7% 1.6% 1.5% 1.3% 1.3% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.7%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.27 \\ 0.48 \\ 0.28 \\ 0.48 \\ 1.62 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.08 \\ 0.$	
2.1.6 Age ~40 Asphar Tofphi2017 HE 2-A2016 HE 2-A2018 HE 2-C2018 HE 2-C2018 Anarzad Sanayei/2022 Sanayei Kong A2016 Zhaowei Kong A2016 Zhaowei Kong A2016 Zhaowei Kong A2016 Hearogeneity: Tau" = 0.35, Test for overall effect: Z = 0. 2.1.7 Intervention duration Asphar Tofphi2017 Ayoub Saeid/2019 Ebrahim Banitalebi-B2018 HE 2-A2018 Morville2018 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2022 P Farzanegi-B2016 Sabtotal (95% CI) Hahashah, Atsubi2020 Zhaowei Kong A2016 Subtotal (95% CI)	250.85 65.714 61.006 66.241 338 950.31 338 950.31 331 (P = 22. 250.85 254.6 65.744 250.85 254.6 65.744 46 66.241 176.31 65.774 46 66.241 176.31 65.714 46 66.241 176.31 65.714 46 66.241 176.31 65.714 46 66.241 176.31 65.714 46 7.20 7.20 9.6 6 7.20 9.6 7.20 9.6 176.31	59,831 59,7577 59,7577 12, df = 7 (76) 4,44 13,258 94,22 59,831 59,7577 82,295 11 28,62 21,41 0,7 4,09, df = 9 01) 94,22 91,8 1,001,45 11,01,45	17 17 17 11 19 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 0002); I [≠] = 265.93 281.6 204.67 74 393.43 364.71 0.6 0.00001); 204.67 7275 692.32 204.67 275 205.05 204.67	25.937 35.121 42.948 680,94 0.6 685% 6.62 5.5 6.62 25.937 35.121 111.36 25.937 35.121 111.36 25.937 35.121 111.36 19.55 0.6 (178.8 680,94 111.36 (28.94) 19.55 0.6 (28.94) 19.55 0.6 (28.94) 19.55 0.6 (29.94) 19.55 0.55 0.6 (29.94) 19.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	1.8% 1.8% 1.7% 1.7% 1.6% 13.8% 1.5% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.5%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.48 \\ (= 20, 1.16) \\ 0.47 \\ (= 22, 1.42) \\ 0.28 \\ (= 55, 1.13) \\ 0.28 \\ (= 55, 1.13) \\ 0.28 \\ (= 55, 1.13) \\ 0.00 \\ (= 48, 0.88) \\ 0.00 \\ (= 48, 0.88) \\ 0.00 \\ (= 42, 0, 0.88$	
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2.1.6 Age ~40 Aghar Tofphi2017 HE 2-A2016 HE 2-A2018 HE 2-C2018 HE 2-C2018 Hanzad Sanayei/2022 Mahzad Sanayei/2022 Manowei Kong A2016 Thioweik Kong A2016 Thioweik Kong A2016 Harorogeneity: Tau" = 0.35; Test for overall effect: Z = 0. 2.1.7 Intervention duration Aghar Tofphi2017 Ayoub Saeid/2019 Eraham Banitalebi-B2018 HE 2-A2018 HE 2-A2018 HE 2-C2018 Morville2018 P Farzanegi-B2022 P Farzanegi-B2025 P Farz	$\begin{array}{c} 250.85\\ 65.714\\ 61.006\\ 66.241\\ 338\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.6\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5\\ 0.5$	59.831 59.7577 82.295 59.7577 82.295 59.7577 82.295 0.4 0.7 780 0.4 740 760 0.4 76000000000000000000000000000000000000	17 17 17 11 19 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 0002); I [≠] = 265.93 281.6 204.67 74 393.43 364.71 0.6 0.00001); 204.67 7275 692.32 204.67 275 205.05 204.67	25.937 35.121 42.948 680,94 0.6 685% 6.62 5.5 6.62 25.937 35.121 111.36 25.937 35.121 111.36 25.937 35.121 111.36 19.55 0.6 (178.8 680,94 111.36 (28.94) 19.55 0.6 (28.94) 19.55 0.6 (28.94) 19.55 0.6 (29.94) 19.55 0.55 0.6 (29.94) 19.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	1.8% 1.8% 1.7% 1.7% 1.6% 1.5% 1.3% 1.3% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.7%	$\begin{array}{c} 0.85 \\ 0.85 \\ 0.48 \\ (-20, -1.60 \\ 0.47 \\ (-22, -1.60 \\ 0.28 \\ (-35, -1.33 \\ 0.32 \\ (-32, -1.33 \\ 0.00 \\ (-38, 0.88) \\ 0.00 \\ (-$	
2.1.6 Age <40 Asphar Tofphi2017 HE 2-A2016 HE 2-A2018 HE 2-C2018 HE 2-C2018 Harbzd Samayei2022 Janowei Kong A2016 Danowei Kong A2017 Ayoub Saei/2019 Erzahog Bantalebi-82018 HE 2-A2018 HE 2-A2018 HE 2-A2018 HE 2-A2018 HE 2-A2018 Morville2018 Danowei Kong A2016 Danowei	$\begin{array}{l} 250.85\\ 65.714\\ 61.006\\ 66.241\\ 950.31\\ 338\\ 0.5\\ 0.5\\ 0.6\\ 0.5\\ 31(P=0.0)\\ 254.6\\ 176.31\\ 46.0\\ 0.5\\ 274.7\\ 289\\ 289\\ 0.5\\ 289\\ 289\\ 289\\ 0.5\\ 176.31\\ 176.31\\ 176.31\\ 191\\ 950.31\\ 191\\ 194.6\\ 0.5\\ 0.5\\ Chi^{9}=6.6\\ 35(P=0.0)\\ 184.6\\ 0.5\\ 0.5\\ 191\\ 184.6\\ 0.5\\ 0.5\\ 191\\ 184.6\\ 0.5\\ 0.5\\ 191\\ 191\\ 191\\ 191\\ 191\\ 191\\ 191\\ 19$	59.831 59.7577 82.285 59.7577 82.285 339.990 0.4 13.358 9.4 4.44 13.258 9.422 59.831 11 28.622 59.831 11 28.62 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 94.22 21.41 0.7 91.8 94.20 21.41 0.7 91.8	17 17 17 17 11 19 109 P = 0.1 109 109 P = 0.1 109 12 17 17 17 17 17 17 17 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 0.0002); I [≠] = 265.93 281.6 36.966 34.407 74 36.976 34.407 74 36.966 34.407 75 692.32 142.9 0.5 6); I [≠] = 4	25937 42.948 680,94 0.6 668% 6.62 5.5 111.36 6.62 5.5 111.36 25.937 35.121 42.948 42.948 20 33.39 19.55 0.6 178.84 20 33.39 19.55 0.6 178.54 19.55 0.6 0.6 19.55 0.6 19.55 0.6 19.55 0.6 19.55 0.6 19.55 0.6 19.55 0.6 19.55 0.6 0.6 19.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	1.8% 1.8% 1.7% 1.7% 1.6% 1.5% 1.3% 1.3% 1.8% 1.8% 1.8% 1.8% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 1.7%	$\begin{array}{c} 0.65 \\ 0.65 \\ 0.46 \\ 1.62 \\ 0.27 \\ 0.48 \\ 0.28 \\ 0.48 \\ 1.62 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.48 \\ 0.08 \\ 0.$	
	250.85 65.714 61.006 66.241 950.31 338 0.5 66.241 950.31 2550.85	59.831 59.7577 82.285 1,001.45 59.7577 82.285 0,014.5 7 12, df = 7 (7 7 6) 12, df = 7 (7 7 7 7 7 7 82.295 11, df = 7 (7 7 82.295 11, df = 7 (7 7 82.295 11, df = 7 (7 7 82.295 11, df = 7 (7 7 82.295 11, df = 7 (7 84.244 10, df = 7 (7 84.245 11, df = 7 (7 84.245) 14, df = 7 (7 84.255) 14, df = 7 (7 84.255) 1	17 17 17 17 11 19 109 P = 0.1 109 109 P = 0.1 109 12 17 17 17 17 17 17 17 17 17 17	36.078 36.966 34.407 692.32 251 0.5 0.6 0.0002); I [≠] = 265.93 281.6 36.966 34.407 74 36.976 34.407 74 36.966 34.407 75 692.32 142.9 0.5 6); I [≠] = 4	25937 42.948 680,94 0.6 668% 668% 668% 668% 668% 668% 75.5 51113.6 25.937 35.121 42.948 20 33.39 19.55 0.6 178.69 4 111.36 678.94 19.55 0.6 10.55 0.6 19.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	17 17 17 11 19 10 8 109 10 12 17 17 17 17 17 17 17 17 17 17 17 17 17	1.8% 1.8% 1.7% 1.7% 1.7% 1.8% 1.5% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.8	$\begin{array}{c} 0.85 \\ 0.85 \\ 0.48 \\ (-20, -1.60 \\ 0.47 \\ (-22, -1.60 \\ 0.28 \\ (-35, -1.33 \\ 0.32 \\ (-32, -1.33 \\ 0.00 \\ (-38, 0.88) \\ 0.00 \\ (-$	

Figure 3: Forest map of subgroup analysis

Further the subgroup analysis was conducted according to the four covariates in Meta-regression to explore the regulation of exercise on FGF21. As shown in Figure. 3, the subgroup analysis indicate that the up-regulation of FGF21 by exercise was related to the subject population. Disease populations, such as type 2 diabetes patients, had a significant combined effect size [SMD = -1.51, 95%CI: -2.89 to -0.13, p = 0.03], indicating a significant difference. Regardless of the subject's BMI, the results were statistically different. The combined effect size for BMI \geq 28 was [SMD = -1.91, 95%CI: -2.91 to -0.91, p = 0.0002], and for BMI < 28, it was [SMD = 0.32, 95%CI: -0.01 to -

0.65, p = 0.05]. The upregulation of FGF21 by exercise was also related to age, with a significant combined effect size [SMD = -1.20, 95%CI: -2.13 to -0.26, p = 0.01] when the subject's age was 40 years or older. When the exercise intervention duration was \geq 40min, the combined effect size was [SMD = -1.21, 95%CI: -2.18 to -0.25, p = 0.01], indicating a significant difference.

4.2. Publication Bias Analysis

As shown in the funnel plot (Figure 4), the 17 included studies can be considered unbiased.

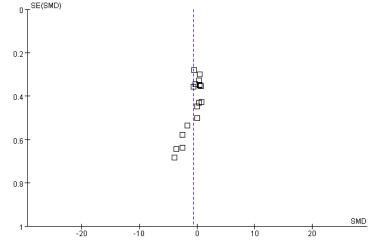


Figure 4: Funnel plot of publication bias

5. Discussion

FGF21 is a novel metabolic regulator whose expression in the liver is primarily regulated by peroxisome proliferator-activated receptor α (PPAR α) [21-24]. Liver-specific knockout of the FGF21 gene in mice results in a significant decrease in circulating FGF21 levels, leading to varying degrees of metabolic syndrome in the mice. In mice models of diabetes, knockout of the FGF21 gene exacerbates insulin resistance caused by diabetes [12, 25-27]. These studies demonstrate the essential role of the liver factor FGF21 in maintaining and protecting the physiological health.

This study shows that exercise intervention can significantly and effectively enhance the levels of FGF21 in adults circulating blood, and this increase is related to exercise duration, and the presence of disease, as demonstrated by meta-analysis. Exercise interventions lasting longer than 40min improved circulating blood levels of FGF21. In healthy adults younger than 48, exercise interventions did not appear to lead to an increase in FGF21. In addition, BMI was also associated with exercise effects, and an increase in FGF21 levels in overweight and obese individuals as a result of exercise intervention was not observed in the general population. In summary, the effect of exercise on improving FGF21 is evident in patients with obesity or metabolic syndrome and appears to be due to the effect of exercise on fat or metabolism-related tissues, inducing tissues to indirectly promote the release of FGF.

Since FGF21 can play an effective role in regulating the body's metabolism, especially fat metabolism, it may play an important role in improving motor processes in people with metabolic disorders. The mechanism by which exercise intervention promotes the release of FGF21 is still unclear, but there is no doubt that exercise improves the metabolic status of target tissues and target cells by increasing FGF21 levels in circulating blood. A complete exercise regimen consists of exercise intensity, exercise load, exercise time, and exercise mode, and subtle variations in different exercise times or exercise intensities [28] can lead to different adaptations in the body. However,

few studies have investigated whether different exercise types and exercise strategies have different effects on FGF21. When more research emerges in the future, meta-analysis can be used to find the most suitable exercise regimen for upregulating FGF21, providing a theoretical basis for future clinical treatment. The differences in FGF21 half-life or secretion duration among the studies included in this paper may have affected the results [14, 29].

Another consideration of the effect of exercise intervention on FGF21 is the change in the expression level of its cofactor β -Klotho. β -Klotho is an important part of the transmembrane protein Klotho group. Which is widely distributed in FGF21 target tissues. However, due to the complexity of the relationship between β -Klotho and FGF21, and the influence of various factors on exercise intervention [30-33], the mechanism needs further exploration.

6. Conclusions

Exercise interventions significantly and effectively enhance FGF21 levels in circulating blood in adults. Our meta-analysis provides a clinical theoretical basis for the regulation of FGF21 through exercise interventions. However, there is limited research on exercise intervention related to FGF21, and the mechanism of FGF21 upregulation is complex, which requires more studies to confirm this theoretical basis.

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