

SUPPLEMENTARY APPENDIX:**Details of Search Strategy**Ovid

Database(s): Embase 1988 to 2013 Week 28, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2013, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2013

Search Strategy:

#	Searches	Results
1	Fatty Liver/	34015
2	exp nonalcoholic fatty liver/	10820
3	("fatty liver" or steatohepatitis or ((NAFLD or NASH) and (liver* or hepat*)) or steatohepatitides or (liver adj2 steatos*) or "visceral steatos*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui, tx, ct]	53319
4	1 or 2 or 3	53319
5	Prognosis/	732245
6	disease course/	275761
7	disease progression/	383328
8	exp treatment outcome/	1648861
9	(outcome* or "natural history" or prognos* or progression or (disease adj3 course) or (disease adj3 evolution)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui, tx, ct]	4710658
10	or/5-9	4767844
11	4 and 10	11780
12	exp controlled study/	4168131
13	exp randomized controlled trial/	709672
14	((control\$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui, tx, ct]	5388418
15	meta analysis/	117927
16	meta-analys\$.mp.	191750
17	exp "systematic review"/	62017
18	(systematic* adj review\$).mp.	149408
19	exp Cohort Studies/	1579728

20	exp prospective study/	656470
21	(prospective adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	793561
22	cohort*.mp.	721146
23	or/12-22	7253882
24	11 and 23	3821
25	from 11 keep 7438-11600	4163
26	limit 25 to (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews) [Limit not valid in Embase,CCTR,CDSR; records were retained]	240
27	24 or 26	3844
	limit 27 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	135
29	27 not 28	3709
30	from 11 keep 11601-11780	180
31	29 or 30	3811
	limit 31 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	3492
33	limit 32 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	2062
34	limit 33 to yr="1985 -Current"	2052
35	remove duplicates from 34	1469

Scopus

- 1 TITLE-ABS-KEY("fatty liver" or steatohepatitis or ((NAFLD or NASH) and (liver* or hepat*)) or steatohepatitides or (liver W/2 steatos*) or "visceral steatos*")
- 2 TITLE-ABS-KEY(outcome* or "natural history" or prognos* or progression or (disease W/3 course) or (disease W/3 evolution))
- 3 TITLE-ABS-KEY((meta W/1 analys*) OR (systematic* W/2 review*) OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*) or cohort* OR "prospective stud*" OR "prospective survey*" OR "prospective analys*")
- 4 PUBYEAR Aft 1984
- 5 1 and 2 and 3 and 4
- 6 TITLE(child* or adolescent* or infant*)
- 7 TITLE(adult or adults)
- 8 6 and not 7
- 9 5 and not 8
- 10 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
- 11 9 and not 10
- 12 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 13 11 and not 12

Web of Science

- 1 Topic=("fatty liver" or steatohepatitis or ((NAFLD or NASH) and (liver* or hepat*)) or steatohepatitides or (liver NEAR/2 steatos*) or "visceral steatos*") AND Topic=(outcome* or "natural history" or prognos* or progression or (disease NEAR/3 course) or (disease NEAR/3 evolution)) AND Topic=((meta NEAR/1 analys*) OR (systematic* NEAR/2 review*) OR (control* NEAR/2 stud*) OR (control* NEAR/2 trial*) OR (randomized NEAR/2 stud*) OR (randomized NEAR/2 trial*) or cohort* OR "prospective stud*" OR "prospective survey*" OR "prospective analys*") Timespan=1985-2013. Databases=SCI-EXPANDED.
- 2 TI=(child* or adolescent* or infant*) NOT TI=(adult or adults)
Databases=SCI-EXPANDED Timespan=1985-2013
- 3 (#1 not #2) AND Document Types=(Article OR Abstract of Published Item OR Meeting Abstract OR Proceedings Paper) Databases=SCI-EXPANDED Timespan=1985-2013

Figure Legends:**Supplementary Figure 1.** Flowchart summarizing study identification and selection

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Author, year of publication	Location	Duration	Histologic staging system	Active treatment arm; No. of patients	Placebo arm intervention; No. of patients (total/no. with paired biopsies)	Change in fibrosis scores in placebo-treated patients		
						Worsened	Stable	Improved
Abdelmalek, 2009	MN and FL, USA	12m	Brunt	Betaine; 17	Placebo and Diet+Exercise counseling; 28/18	7 (39%)	8 (44%)	3 (17%)
Aithal, 2008	Nottingham, UK	12m	Brunt	Pioglitazone; 31	Placebo and diet+exercise counseling; 37/30	6 (20%)	18 (60%)	6 (20%)
Ratziu, 2008	France	12m	Brunt	Rosiglitazone; 32	Placebo and diet+exercise counseling; 31/31	6 (19%)	20 (65%)	5 (16%)
Sanyal, 2010	USA	24m	NASH-CRN	Vitamin E or pioglitazone; 164	Placebo and diet+exercise counseling; 83/72	16 (22%)	34 (47%)	22 (31%)
Van Wagner, 2011	IL, USA	12m	Brunt	Pentoxifylline ; 19	Placebo and diet+exercise counseling; 7/7	3 (43%)	4 (57%)	0

[Abbreviations: No.- number, NASH-CRN-Nonalcoholic steatohepatitis Clinical Research Network, NAFLD-nonalcoholic fatty liver disease]

Supplementary Table 1. Details of patients included in control arm of placebo-controlled randomized controlled trials of NAFLD therapy. Please note that all participants in these trials had NASH.

		Final fibrosis Stage					Total stages of fibrosis progressed	Person-years of follow-up
Non-Alcoholic Fatty Liver Disease (2 studies) – All patients had non-alcoholic steatohepatitis								
		0	1	2	3	4		
Baseline fibrosis stage	0 (8)	6	0	1	1	0	+5	8
	1 (9)	0	5	1	2	1	+8	9
	2 (4)	0	1	1	1	1	+1	4
	3 (7)	1	1	0	5	0	-5	8
	4 (0)	0	0	0	0	0	0	0
	Overall (28)						+9	28
	Stage 0 plus Stage 1 fibrosis (17)						+13	17

Supplementary Table 2. Overall fibrosis progression rate by baseline fibrosis stage in patients with nonalcoholic steatohepatitis, enrolled in control arm of placebo-controlled randomized controlled trials.

Study	NAFLD	NAFL	NASH
Adams 2005(6)	(1) Steatosis involving at least 10% of hepatocytes on biopsy, (2) ethanol consumption of less than 140 g/week, (3) exclusion of patients with evidence of other liver disease using standard clinical, laboratory and histological criteria.	Combination of steatosis with non-specific inflammation (steatosis plus either lobular inflammation or Ballooning, but not both) or bland steatosis (steatosis without lobular inflammation, ballooning or fibrosis)	Either the presence of steatosis plus mixed lobular inflammation plus hepatocellular ballooning, or the presence of steatosis plus any stage of fibrosis
Argo 2009(21)	Only patients with NASH	-	NASH characterized by fatty infiltration, inflammation, and variable degrees of fibrosis, Mallory hyaline, and apoptotic bodies
Ekstedt 2006(7)	Hepatic steatosis without any other concomitant liver disease, weekly alcohol consumption <140g or medication associated with fatty infiltration of the liver	Simple steatosis or steatosis with non-specific inflammation and absence of fibrosis	Steatosis plus any stage of fibrosis or as steatosis plus lobular inflammation plus ballooning degeneration
Evans 2002(22)	Only patients with NASH	-	Non-alcoholic steatosis with necroinflammation and/or fibrosis
Fassio 2004(23)	Only patients with NASH	-	Non-alcoholic macrovesicular steatosis (> 10% of hepatocytes) and lobular inflammation plus ballooning degeneration, Mallory hyaline fibrosis, sinusoidal fibrosis, or a combination thereof.
Hamaguchi 2010(24)	Hepatic steatosis in the absence of known causes of fatty liver	Hepatic steatosis without presence of ballooned hepatocytes	Hepatic steatosis along with ballooned hepatocytes with lobular hepatitis
Hui 2005(25)	Histological evidence of steatosis with or without the presence of necroinflammation and fibrosis, without known causes of fatty liver	Simple steatosis without necroinflammation or fibrosis	Hepatic steatosis with some necroinflammatory activity and/or fibrosis
Pais 2013(12)	Hepatic steatosis >10% in the absence of known causes of fatty liver	Hepatic steatosis alone (bland steatosis) or steatosis without evidence of ballooning, with spotty lobular inflammation of grade 1 maximum (<2 foci/sox power field) and no fibrosis or fibrosis limited to mild periportal or perisinusoidal fibrosis	Hepatic steatosis (>5%) co-existing with hepatocellular ballooning and lobular necroinflammation, with or without fibrosis
Ratziu 2000(26)	Abnormal liver enzymes in overweight or obese patients, after exclusion of other causes of liver diseases	Not adequately reported	Not adequately reported
Teli 1995(11)	Hepatic steatosis in the absence of excessive alcohol use	Hepatic steatosis, with no features of steatohepatitis and fibrosis	-
Wong 2010(27)	Histological evidence of steatosis with or without the presence of necroinflammation and fibrosis, without known causes of fatty liver	Fatty liver alone without necroinflammation	Hepatocyte ballooning or intralobular hepatocyte necrosis

[Abbreviations: NAFLD-nonalcoholic fatty liver disease, NAFL- nonalcoholic fatty liver, NASH- nonalcoholic steatohepatitis]

Supplementary Table 3. Definitions of NAFLD, NAFL and NASH in included studies

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Question	Scoring scheme	Adams(6)	Argo(21)	Ekstedt(7)	Evans(22)	Fassio(23)	Hamaguchi(24)	Harrison (41)	Hui(25)	Pais(12)	Ratziu(26)	Teli(11)	Wong(27)	Abdelmalek(28)
Representative of the average adult in the community	1 point for unselected participants in population-based or multicenter studies, 0.5 points for unselected participants in single-center hospital-based study; 0 points for participants in an RCT or selective cohort	0.5	0.5	1	0.5	0.5	0.5	1	0.5	0.5	0	0.5	0.5	0
Large cohort size	1 point if cohort size >50 patients with baseline and follow-up biopsies, 0.5 points if cohort size between 25-50 patients, 0 points if cohort size of <25 patients	1	0	1	0	0.5	0.5	0	0	0.5	0	0	1	0
Histological confirmation of NAFLD	1 point if standardized assessment of NAFLD with information on NASH and/or NAFL separately, 0.5 points if standardized assessment of NAFLD, without distinction between NASH or NAFL, 0 points if reviewed only non-standardized classification of NAFLD	0.5	1	1	1	1	1	1	1	1	0.5	0	1	1
Histological assessment of fibrosis progression	1 point if assessed using Brunt classification or NASH-CRN, 0.5 point if assessed using Ishak or Metavir classification, 0 point if assessed using non-standardized classification	1	1	1	1	0.5	0.5	1	1	1	0.5	0	1	1
Adequate follow-up of cohort for outcome to occur	1 point if mean follow-up of entire cohort >5 years, 0.5 points if cohort follow-up between 3-5 years, 0 points if mean follow-up of cohort <3 years	0.5	0.5	1	1	1	0	1	1	0.5	0.5	1	0.5	0
Attrition rate	1 point if >80% of cohort followed-up, 0.5 points if 50-80% cohort followed-up, 0 points if >50% lost to follow-up or not reported how many patients with NAFLD seen in clinic	0	0.5	0.5	0	0	0	0	0	0	0	0	1	0.5
Information on potential disease-modifying therapy adopted by participants	1 point if adequate information on lifestyle modification as well as medication use, 0.5 points if incomplete information, 0 points if no information on adoption of disease-modifying therapy	0.5	1	0	0	1	1	0	0.5	0.5	0	0	1	1
Reported risk factors associated with progression of fibrosis	1 point if factors studied in multivariate models, 0.5 points if factors reported in only in univariate models, 0 points if factors associated with fibrosis progression not reported	1	0.5	1	0	1	1	0.5	0.5	1	0	0	1	0
Total Score (Maximum = 8; High quality ≥6; Medium quality 3-5 and low quality ≤2)		5	5	6.5	3.5	5.5	4.5	4.5	4.5	5	1.5	1.5	7	3.5

[Abbreviations: NAFLD-nonalcoholic fatty liver disease, NAFL- nonalcoholic fatty liver, NASH- nonalcoholic steatohepatitis]

Supplementary Table 4. Quality of included studies.

Study			Final fibrosis stage					Fibrosis progression	PY FU
			F0	F1	F2	F3	F4		
Adams(6)	Initial fibrosis stage	F0 (25)	13	5	3	2	2	+25	80
		F1 (21)	7	2	8	4	0	+9	67.2
		F2 (23)	4	4	5	7	3	+1	73.6
		F3 (18)	2	1	6	5	4	-10	57.6
		F4 (16)	0	0	1	5	10	-7	51.2
	Overall							+18	329.6
			Final fibrosis stage						
Argo(21)	Initial fibrosis stage	F0 (0)	0	0	0	0	0	0	0
		F1 (1)	0	0	1	0	0	+1	4.4
		F2 (2)	1	1	0	0	0	-3	8.8
		F3 (2)	0	0	0	0	2	+2	4.4
		F4 (0)	0	0	0	0	0	0	0
	Overall							0	22
			Final fibrosis stage						
Ekstedt(7)	Initial fibrosis stage	F0 (36)	19	8	6	3	0	+29	496.8
		F1 (19)	5	9	3	1	1	+3	262.2
		F2 (11)	0	5	1	2	3	+3	151.8
		F3 (4)	0	0	1	1	2	+1	55.2
		F4 (0)	0	0	0	0	0	0	0
	Overall							+36	1202
			Final fibrosis stage						
Evans(22)	Initial fibrosis stage	F0 (4)	2	1	1	0	0	+3	32.8
		F1 (1)	0	0	1	0	0	+1	8.2
		F2 (2)	0	0	1	1	0	+1	16.4
		F3 (0)	0	0	0	0	0	0	0
		F4 (0)	0	0	0	0	0	0	0
	Overall							+5	57.2
			Final fibrosis stage						
Fassio(23) (Ishak staging)	Initial fibrosis stage	F0 (3)	2	0	0	0	1	+4	15.9
		F1 (11)	0	8	0	3	0	+6	58.3
		F2 (4)	0	2	1	1	0	-1	21.2
		F3 (4)	0	2	0	0	2	-2	21.2
		F4 (0)	0	0	0	0	0	0	0
	Overall							+7	116.6
			Final fibrosis stage						
Hamaguchi (24)(some reported as 1.5 stage)	Initial fibrosis stage	F0 (0)	0	0	0	0	0	0	0
		F1 (24)	3	10	10	1	0	+10	57.6
		F2 (6)	0	4	2	0	0	-4	14.4
		F3 (5)	0	2	2	1	0	-6	12
		F4 (4)	0	0	0	1	3	-1	9.6
	Overall							-1	93.6
			Final fibrosis stage						
Hui(25)	Initial	F0 (11)	5	5	1	0	0	+7	67.1

	fibrosis stage	F1 (5)	0	3	2	0	0	+2	30.5
		F2 (1)	0	0	0	0	1	+2	6.1
		F3 (0)	0	0	0	0	0	0	0
		F4 (0)	0	0	0	0	0	0	0
	Overall							+11	97.8
		Final fibrosis stage							
Pais(12)		F0	F1	F2	F3	F4			
	Initial fibrosis stage	F0 (10)	6	3	1	0	+7 (approx)	37	
		F1 (10)	0	1	5	4	+13	37	
		F2 (5)	0	0	4	1	+1	18.5	
		F3 (0)	0	0	0	0	0	0	
	F4 (0)	0	0	0	0	0	0		
	Overall							+21	102.7
		Final fibrosis stage							
Ratziu(26)		F0	F1	F2	F3	F4			
	Initial fibrosis stage	F0 (4)	4	0	0	0	0	20.8 (mean FU 5.2 inferred from total py)	
		F1 (10)	4	4	1	0	1	52	
		F2 (0)	0	0	0	0	0	0	
		F3 (0)	0	0	0	0	0	0	
	F4 (0)	0	0	0	0	0	0		
	Overall							0	73
		Final fibrosis stage							
Teli(11)		F0	F1	F2	F3	F4			
	Initial fibrosis stage	F0 (12)	11	0	1	0	0	+2	139.2
		F1 (0)	0	0	0	0	0	0	0
		F2 (0)	0	0	0	0	0	0	0
		F3 (0)	0	0	0	0	0	0	0
	F4 (0)	0	0	0	0	0	0	0	
	Overall							+2	139.2
		Final fibrosis stage							
Wong(27)		F0	F1	F2	F3	F4			
	Initial fibrosis stage	F0 (26)	17	7	0	1	1	+14	78
		F1 (17)	7	7	1	2	0	-2	51
		F2 (7)	4	1	0	1	1	-6	21
		F3 (1)	0	0	1	0	0	-1	3
	F4 (1)	0	0	0	0	1	0	3	
	Overall							+5	156

Supplementary Table 5. Fibrosis progression in individual studies

Location	Baseline fibrosis stage	NAFLD	NAFL	NASH
Western (8 studies)	Stage 0	0.12 (0.06-0.18)	0.05 (0.00-0.10)	0.14 (0.00-0.29)
	Stage 1	0.13 (0.04-0.23)	0.35 (0.20-0.50)	0.06 (-0.02-0.14)
	Stage 0 or 1	0.12 (0.06-0.17)	0.09 (0.02-0.15)	0.08 (-0.01-0.17)
Asian (3 studies)	Stage 0	0.14 (0.07-0.21)	0.11 (0.01-0.22)	0.17 (0.03-0.31)
	Stage 1	0.06 (-0.06-0.18)	0.06 (-0.19-0.32)	0.33 (-0.04-0.71)
	Stage 0 or 1	0.10 (0.07-0.14)	0.09 (0.04-0.14)	0.14 (0.07-0.21)

[Abbreviations: NAFLD-nonalcoholic fatty liver disease, NAFL- nonalcoholic fatty liver, NASH-nonalcoholic steatohepatitis]

Supplementary Table 6. Subgroup analysis comparing rates of fibrosis progression in Western and Asian population

Study	Adams ^a (6)		Ekstedt(7)		Fassio(23)		Hamaguchi ^a (24)		Harrison ^b (36)		Hui(25)		Wong(27)	
	PR (38)	Non-PR (35)	PR (29)	Non-PR (41)	PR (7)	Non-PR (15)	PR (11)	Non-PR (16)	PR (7)	Non-PR (15)	PR (9)	Non-PR (8)	PR (14)	Non-PR (38)
Age (mean±SD)	44±2	47±2	61±11	60±11	49±12	44±11	51±9	48±15	49	51	46±8	36±7	45±10	44±9
Male sex (n)	13	16	21	29	2	7	5	12	6	7	5	6	9	25
Diabetes (n)	20	15	15	24	4	4	7	11	3	6	2	2	6	20
Hypertension (n)	12	10	28	38			4	3	6	5	0	0	9	17
Obesity (n), or mean±SD	28	22	29.6 ±3.3	28.3 ±5.3	6	4*	30.9 ±3.6	27.5 ±2.5	31.8	34.7	29.8 ±2.9	27.2 ±3.7	27.7 ±4.4	27.3 ±3.4
Metabolic syndrome (n)	19	20	18	21	-	-	3	7*	-	-	-	-	8	27
AST (mean±SD)	71±34	74±44	42±17	31±13*	-	-	32 ±17	29 ±18	76	40*	-	-	-	-
ALT (mean±SD)	104±60	94±51	75±44	51±25	70±10	73±22	40 ±38	48 ±14	95	64	128 ±41	90 ±35	51±15	63±16
AST/ALT ratio (mean±SD)	0.8±0.3	0.9±0.4	0.6±0.2	0.7±0.4	0.53 ±0.12	0.59 ±0.14	-	-	0.73	0.76	-	-	-	-
Ferritin (mean±SD)	354 ±381	258 ±194	207 ±193	174 ±125	-	-	46 ±84	397 ±103	-	-	-	-	-	-
HOMA-IR (mean±SD)	2.78 ±1.71	4.15 ±3.78	5.2 ±5.3	2.9 ±1.5*	-	-	3.9 ±2.4	3.4 ±1.4	-	-	-	-	1.7 ±0.5	2.1 ±0.5
Platelet count (mean±SD)	228 ±85	197 ±72	205 ±59	252 ±62*	-	-	243 ±52	230 ±80	-	-	-	-	-	-

*-p<0.05 between progressors v. non-progressors; ^acompares progressors to stable repeat biopsy, ^bstudy offers p-value for difference between groups; please note for some studies, instead of standard deviation, range was reported – this was converted to standard deviation using the formula, S.D.=(max-min)/4 (derived from Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13) [Abbreviations: ALT-alanine aminotransferase, AST-aspartate aminotransferase, BMI-body mass index, CI-confidence intervals, HOMA-IR-homeostatic model assessment for insulin resistance, non-PR-patients with no progression of fibrosis, PR-patients with progressive fibrosis, SD-standard deviation]

Supplementary Table 7. Comparison between patients with progressive and non-progressive fibrosis

