# Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection

James B. Maurice<sup>a</sup>, Amee Patel<sup>b</sup>, Alasdair J. Scott<sup>c</sup>, Krish Patel<sup>d</sup>, Mark Thursz<sup>a</sup> and Maud Lemoine<sup>a</sup>

# See related paper on page 1633

**Objective:** To identify the prevalence and risk factors of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and fibrosis in HIV-monoinfected patients.

Design: Systematic review and meta-analysis.

**Methods:** We searched Medline and Embase and included studies that enrolled HIVmonoinfected patients with NAFLD defined by imaging and/or liver histology. Data on prevalence and risk factors for NAFLD, NASH and fibrosis were collected for metaanalysis using random effects models.

**Results:** Ten studies were included from the United States of America (n = 4), Canada (n = 1), France (n = 2), Italy (n = 1), Japan (n = 1) and China (n = 1). The prevalence of NAFLD (Imaging studies), NASH and fibrosis (biopsied populations) were 35% [95% confidence interval (CI) 29–42], 42% (95% CI 22–64) and 22% (95% CI 13–34), respectively. Meta-analysis of risk factors showed that high BMI, waist circumference, type 2 diabetes, hypertension, triglycerides and high CD4<sup>+</sup> cell count were associated with NAFLD, whereas HIV viral load, duration of HIV infection, duration of antire-troviral therapy and CD4<sup>+</sup> cell count nadir were not. Patients with high BMI [mean difference (MD) 1.38, 95% CI 0.04–2.71 P = 0.04], fasting glucose (MD 0.80, 95% CI 0.47–1.13 P < 0.00001) and AST level (MD 13.00, 95% CI 4.34–21.65 P = 0.003) were at increased risk of significant liver fibrosis.

**Conclusion:** NAFLD is frequently observed in HIV-monoinfected patients, and NASH is a common cause of unexplained abnormal liver function in patients selected for liver biopsy. Metabolic disorders are key risk factors independently of HIV parameters. Future trials on pharmacological interventions in NASH with fibrosis should include patients with HIV. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

#### AIDS 2017, 31:1621-1632

# Keywords: antiretroviral therapy, fatty liver, fibrosis, HIV, nonalcoholic fatty liver disease, prevalence, risk factors

# Introduction

The prognosis for HIV-infected patients has significantly improved as HAART are now widely used. As a result, AIDS-related mortality has decreased, but non-AIDS comorbidities including chronic liver disease have emerged as diagnostic and management problems [1]. Among these, nonalcoholic fatty liver disease (NAFLD) has become a new concern in the management of patients with HIV.

NAFLD is defined by liver steatosis, the accumulation of triglycerides in the hepatocytes, in the absence of a secondary cause such as excessive alcohol consumption.

<sup>a</sup>Department of Hepatology, St Mary's Hospital, Imperial College London, <sup>b</sup>GKT School of Medicine, King's College London, <sup>c</sup>Department of Surgery, St Mary's Hospital, Imperial College London, and <sup>d</sup>Barts and the London School of Medicine and Dentistry, Queen Mary University, London, UK.

Correspondence to James B. Maurice, MBChB, BSc, Liver Unit, Department of Hepatology, St Mary's Hospital, Imperial College London, 10th Floor QEQM, Praed St, London W2 1NY, UK.

Tel: +44 02078866454; e-mail: James.maurice@imperial.ac.uk

Received: 15 February 2017; revised: 28 March 2017; accepted: 3 April 2017.

DOI:10.1097/QAD.00000000001504

# ISSN 0269-9370 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

The condition encompasses a spectrum of diseases from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis. In non-HIV patients NAFLD is principally the hepatic manifestation of the metabolic syndrome, occurring in the context of insulin resistance, central obesity and dyslipidaemia [2], with disease progression involving a number of complex interacting factors such as genetic susceptibility, oxidative stress and dysbiosis [3]. The prevalence of NAFLD worldwide is estimated to be 25% and is increasing in conjunction with rising levels of obesity, type 2 diabetes mellitus and the metabolic syndrome [4]. Consequently NAFLD is expected to become the leading cause of liver transplantation over the next decade [5].

Identifying patients at risk of NAFLD, especially severe disease with NASH and fibrosis, is critical. In non-HIV patients, prevalence and risk factors of NAFLD and its complications have been well documented, especially in industrialized countries [6].

By contrast, there are more limited data on NAFLD in the HIV-infected population. The pathophysiology might be even more complex due to additional factors including lipodystrophy and HAART [7], and there is still controversy over the prevalence and risk factors associated with the development of NAFLD, NASH and fibrosis, with studies showing both increased [8] and decreased [9] prevalence compared with the general population.

The aim of this study was to perform a systematic review of the medical literature investigating the prevalence and risk factors for NAFLD, NASH and fibrosis in HIVmonoinfected patients.

# Methods

The systematic review was conducted in accordance with guidance from PRISMA [10]. MEDLINE and EMBASE databases were searched on 14 September 2016 for the terms 'HIV,' 'hepatic steatosis' and related synonyms and keywords (Supplementary Table 1, http://links.lww. com/QAD/B87). Studies were included comparing adult (aged  $\geq 16$  years) HIV-infected populations with and without NAFLD, as defined by imaging [ultrasound, computed tomography (CT), magnetic resonance spectroscopy (H-MRS) or controlled attenuation parameter (CAP)] or liver histology confirming the presence of hepatic steatosis ( $\geq$ 5%) in the absence of viral hepatitis or known excess alcohol consumption. NAFLD with NASH was histologically defined, and significant fibrosis was defined histologically ( $\geq$ F2 according to the Metavir, Ishak or NASH Clinical Research Network scores) or by transient elastography at least 7.0 kPa. Studies including patients with chronic hepatitis B or C or alcohol excess were excluded. Prospective and retrospective observational or interventional studies, randomized controlled trials and systematic reviews were included for review. Non-English abstracts were translated, and the article was requested if the study was possibly relevant. Reference lists of included articles found in the initial database search were also interrogated manually for relevant articles, as well as studies listed as citing included studies on PubMed. Literature reviews, case reports, letters and conference abstracts were excluded.

The results of the search were reviewed by two independent researchers (A.P. and K.P.). Discrepancies in the included studies were resolved by discussion and reviewed by a senior researcher (J.M.) before a final decision on inclusion was made. Data on demographics, diagnostics (prevalence and severity of NAFLD based on imaging and histology) and risk factors for NAFLD was extracted by three independent researchers (A.P., K.P. and J.M.) in duplicate and checked for consistency.

An assessment of included study quality was made using the NIHR Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [11]. Studies could be awarded a maximum 14 points and were reviewed independently by two researchers (J.M. and A.P.). Disagreements were discussed, and a final assessment was made by mutual agreement.

If three or more studies were identified reporting appropriate data on the prevalence or associated risk factors in HIV-infected patients with and without NAFLD, a meta-analysis was performed. Where data were missing or presented in a format that could not be entered into the meta-analysis (e.g. medians with interquartile range), authors were contacted and raw data were requested (for full details of author contact, see Supplementary Table 3, http://links.lww.com/QAD/B87).

### Statistical analysis

Individual study prevalences were logit transformed, and a pooled prevalence calculated by an inverse variance weighted random effects model using the restricted maximum likelihood estimator. Pooled prevalences were back-transformed and projected onto forest plots. 95% confidence intervals (CIs) were calculated by the Clopper–Pearson method [12].

Risk factor meta-analysis required studies to present discrete data for dichotomous variables and mean (SD) for continuous variables to allow the calculation of odds ratios (ORs) and MDs, respectively. Data for grades of steatosis were pooled using weighted means to give values for present and absent steatosis. Data were pooled using a random-effects model to generate summary ORs and MDs with 95% CIs. *P* values were calculated for comparison against the null hypothesis of no effect (OR = 1 or MD = 0). A *P* value less than or equal to 0.05 was considered significant [13].

The  $I^2$  statistic and Cochran's Q test were used to quantify statistical heterogeneity between studies in each model. Where heterogeneity was identified, the reasons for this were explored.

Meta-analysis of risk factors was conducted in Review Manager 5.5 [13], and meta-analysis of prevalence data was conducted in R 3.3.0 (Foundation for Statistic Computing, Vienna, Austria) using the meta and metafor packages [14].

# Results

From 410 studies identified in the literature search, 10 studies were included in the review (Fig. 1). The studies were from the United States America (n = 4) [8,15–17], Canada (n = 1) [18], France (n = 2) [19,20], Italy (n = 1) [21], Japan (n = 1) [22] and China (n = 1) [23]. All were single centre, cross-sectional studies (three with case-control). There were no interventional studies. Five studies diagnosed NAFLD with imaging [liver ultrasound (n = 2) [15,22], CT (n = 1) [21], H-MRS (n = 1) [23] or CAP (n = 1) [18]], and six studies with liver biopsy [8,16–20] [including a subpopulation in a study primarily using ultrasound scan (USS)] [15] (Table 1).

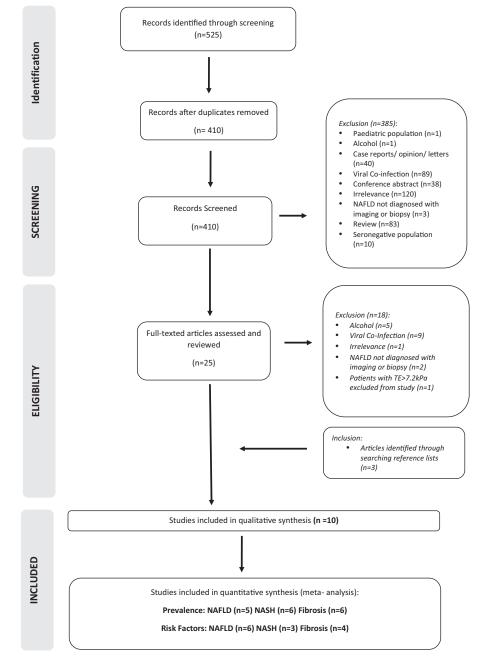


Fig. 1. PRISMA flow diagram for included studies.

Table 1. Sum	mary of in	Table 1. Summary of included studies.	S.						
Author	Year	Country	и	Ethnicity	BMI	Diabetes (%)	Population	Diagnosis of NAFLD	Prevalence of NAFLD, NASH and fibrosis (%)
Crum- Cianflone	2009	USA	$\begin{array}{c} 216\\ (Biopsy\\ n=55) \end{array}$	White 47.7% Black 27.3 Hispanic 13.9 Other 11 1	26.0±4.1	5.1	Consecutive patients in unspecified military hospital clinic. Biopsy offered with abnormal liver enzymes +/or abnormal LISS	USS (liver biopsy in subgroup)	NAFLD: 31.0 NASH: 7.3 ≥F2 Fibrosis: 3.6
Guaraldi	2008	Italy	225		$23.8 \pm 3.4$	13.8	Consecutive patients in metabolic clinic	CT	NAFLD: 36.9 NASH: - >E2 Eibrooid
Ingiliz	2009	France	30	I	$23.0 \pm 3.1$	I	ALT or AST > ULN≥ 2 occasions in previous 6 months	Liver biopsy	ZELZ FILIOUSIS NAFLD: 60.0 NASH: 53.3 >F2 Fibrosis: 20.0
Lemoine	2006	France	14	I	23.0±3.4	I	ALT ≥ 2 × ULN over ≥3 months. Cases: HIV mono- infection ± insulin resistance. Controls: HIV negative NAFLD	Liver biopsy	NAELD: 57.1 NAFLD: 57.1 NASH: 57.1 ≥F2 Fibrosis: 28.6
Lui	2016	China	80	Chinese Asian 93.8%	$23.6 \pm 3.9$	48.8	Consecutive patients in general ID and HIV metabolic clinic. One participant with excess alcohol (>140 o/week)	H-MRS	NAFLD: 28.8 NASH: - ≥F2 Fibrosis: 13.8 (TF > 7 0 kPa)
Morse	2015	USA	62	White 64.5% Black 8.1% Asian 3.2% Other 24.2% Hispanic 29.0%	28.0±4.4	9.7	AST or $ALT > ULN \ge 3$ occasions over $\ge 6$ months	Liver biopsy	NAFLD: 72.6 NASH: 54.8 NASH: 54.8 ≥F2 Fibrosis: 19.4
Nishijima	2014	Japan	435	East Asian 97.5%	$22.8 \pm 3.8$	5.1	All HIV patients with available USS data	NSS	NAFLD: 31.0 NASH: - >F2 Fibrosis
Sterling	2014	NSA	14	White 57.0%	$29.9 \pm 7.4$	0.0	AST or ALT 1.25–5 × ULN over ≥6 months. People with diabetes	Liver biopsy	<ul> <li>ZETZ FILMOSIS</li> <li>NAFLD: 64.3</li> <li>NASH: 28.6</li> <li>&gt;E2 Fibrosis: 35.7</li> </ul>
Vodkin	2015	USA	33	Hispanic 51.5%	$29.8 \pm 6.0$	18.2	Cases: liver biopsies of NAFLD in HIV monoinfecion. Controls: age and sex-matched cases of HIV montive NAFLD	Liver biopsy	ZEZ 10058: 33.3 NAFLD: N/A NASH: 63.6 ≥F2 Fibrosis: 33.3
Vuille- Lessard	2016	Canada	300	White 42.0% Black 40.0% Hispanic 13.7% South Asian 3.3%	26.0±4.3	11.3	Consecutive and unselected HIV mono-infected patients with TE and CAP	CAP	NAFLD: 48.0 NASH: - ≥F2 Fibrosis: 15.0 (LS ≥ 7.1 kPa)
ALT, alanine aminotra proton-magnetic reson USS, ultrasound scan.	aminotrans stic resonan nd scan.	ferase; AST, a	Ispartate amii py; ID, infect	ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI express proton-magnetic resonance spectroscopy; ID, infectious diseases; NAFLD, non USS, ultrasound scan.	sed as mean±5 nalcoholic fatty I.	SD; CAP, contr iver disease; N.	ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI expressed as mean±SD; CAP, controlled attenuation parameter; CT, computed tomography; HC, healthy controls; H-MRS, proton-magnetic resonance spectroscopy; ID, infectious diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TE, transient elastography; ULN, upper limit of normal; USS, ultrasound scan.	uted tomography; HC, ansient elastography; U	healthy controls; H-MRS, LN, upper limit of normal;

Seven authors provided additional data, so it could be incorporated into the meta-analysis [15,17–20,22,23] (Supplementary Table 2, http://links.lww.com/QAD/B87).

# Demographics

The study populations were almost exclusively male (>90% in all studies except one) [18]. In keeping with the geographical location of the studies, there was variation in population ethnicity. The two studies from the Far East had more than 90% East Asian participants, whereas studies in Europe and America included more heterogeneous populations. The proportion of black and Hispanic participants ranged between 8.1–40.0% and 13.7–51.5%, respectively (Table 1).

The mean BMI ranged from 22.8 (imaging study, Japan) [22] to  $29.9 \text{ kg/m}^2$  (biopsy study, the United States of America) [16]. Five studies had a mean BMI less than  $25 \text{ kg/m}^2$ . The prevalence of type 2 diabetes ranged from 0% (diabetes was an exclusion criteria) [16] to 48.8% (recruiting from a metabolic clinic) [23] (Table 1).

Six studies investigated and excluded other causes of chronic liver disease [16–21] One study documented but did not exclude drugs known to cause secondary steatosis [15], and one study explicitly documented exclusion of patients on methotrexate, tamoxifen, amiodarone and steroids [8].

# Study quality

Studies were of moderate-to-poor quality, with scores ranging from 5 to 8 (maximum score 14) according to the NIH Quality Assessment Tool (Supplementary Table 3, http://links.lww.com/QAD/B87). Studies were primarily limited by retrospective, cross-sectional design with no longitudinal follow-up.

# Nonalcoholic fatty liver disease prevalence

To reduce heterogeneity and improve the accuracy of the result, NAFLD prevalence analysis was restricted to studies based on imaging. Five studies including 1256 patients were analysed [15,18,21–23]. Pooled prevalence of NAFLD prevalence was 35.3% (95% CI 28.8–42.5) (Fig. 2). There was significant heterogeneity between individual studies ( $I^2 = 85.3\% P < 0.001$ ).

# Nonalcoholic steatohepatitis prevalence

Six studies including 208 cases with histological confirmation of NASH were analysed [8,15–17,19,20]. The pooled prevalence of NASH was 41.7% (95% CI 22.3–64.0). There was significant heterogeneity between individual studies ( $I^2 = 83.1\% P < 0.0001$ ) (Fig. 2), which may be a consequence of variation in patient selection for liver biopsy (Table 1). Liver histology findings are summarized in Supplementary Table 4, http://links. lww.com/QAD/B87.

# **Fibrosis prevalence**

Six studies with 208 cases with data on significant fibrosis, defined by at least F2 fibrosis on liver histology, were included [8,15–17,19,20]. Pooled prevalence of significant fibrosis was 21.7% (95% CI 13.1–33.7) (Fig. 2). The results were more consistent across studies, but significant heterogeneity remained ( $I^2 = 59.3\% P = 0.031$ ).

In addition, two studies included data on the noninvasive assessment of significant liver fibrosis in nonbiopsied populations, but there were insufficient data for metaanalysis. Liu *et al.* reported that in patients with NAFLD and HIV, one of 23 (4.3%) had FIB-4 score 2.67 or more and six of 23 (27.3%) had significant fibrosis defined by increased liver stiffness on transient elastography ( $\geq$ 7.0 kPa). Vuille-Lessard *et al.* did not separate patients with and without NAFLD for their fibrosis assessment but reported FIB-4 score 2.67 or more in 20 of 300 (6.7%) and increased liver stiffness ( $\geq$ 7.1 kPa) in 45 of 300 (15%) in the whole cohort of HIV-monoinfected patients [18,23].

# Risk factors for nonalcoholic fatty liver disease

Six studies provided data on the risk factors for NAFLD in HIV-monoinfected patients with sufficient data to perform meta-analysis on 17 variables [15,16,18,21–23].

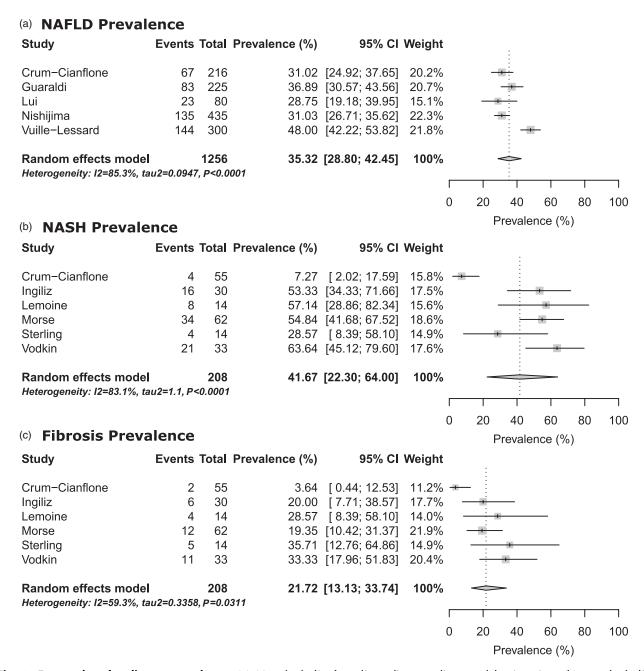
BMI (MD 2.92 95% CI 2.14-3.70, P<0.00001), waist circumference [MD 8.05 (5.46–10.64) P < 0.00001], type 2 diabetes [OR 1.61 (1.09–2.39) P = 0.02], hypertension [OR 1.75 (1.27–2.41) P = 0.0006], high triglycerides [MD 61.52 (24.31–98.74) P = 0.001], high total cholesterol [MD 6.19 (0.93–11.45) P=0.02], low HDL cholesterol [MD -4.21 (-6.82 to -1.59) P = 0.002], high LDL cholesterol [MD 5.80 (2.01–9.58) P = 0.003], high fasting glucose [MD 0.43 (0.18–0.68) P=0.0007], high alanine aminotransferase [MD 15.98 (8.04-23.92) P < 0.0001, high aspartate aminotransferase (AST) [MD 5.27 (2.66–7.88) P < 0.0001] and high CD4<sup>+</sup> T-cell count [MD 54.83 (11.55–98.11) P=0.0]) were associated with NAFLD. Age, suppressed HIV viral load, duration of HIV infection, duration of HAART and CD4<sup>+</sup> nadir were not associated with NAFLD (Fig. 3). There were insufficient data to meta-analyse the diagnosis of dyslipidaemia (based on the use of lipid-lowering drugs).

There was significant statistical heterogeneity between studies for BMI ( $I^2 = 56\% P = 0.04$ ), triglycerides ( $I^2 = 73\%, P = 0.001$ ) and HDL ( $I^2 = 55\%, P = 0.05$ ).

Sensitivity analysis with data restricted to imaging studies alone, and with Crum-Cianflone USS data replaced with their biopsy data, did not change any of the outcomes relationship with NAFLD (data not shown).

# Risk factors for nonalcoholic steatohepatitis and fibrosis

Three studies provided data for meta-analysis on patients with a histological diagnosis of NASH [15,17,19]. None



**Fig. 2. Forest plots for disease prevalence.** (a) Nonalcoholic fatty liver disease, diagnosed by imaging; (b) nonalcoholic steatohepatitis, diagnosed by liver biopsy; (c) significant fibrosis, defined as at least F2 fibrosis diagnosed by liver biopsy.

of the reported parameters were associated with NASH, although the studies were small in size (141 cases) with data available on only limited variables (Supplementary Fig. 1, http://links.lww.com/QAD/B88).

Four studies provided data on 11 risk factors for significant fibrosis (defined as  $\geq$ F2 fibrosis on liver biopsy or  $\geq$ 7.1 kPa by transient elastography) including 379 cases. Data were not included from Liu *et al.* as factors associated with fibrosis were assessed in a population with HIV-positive and HIV-negative cases. Three studies were based on liver histology [15,17,19], but the results were

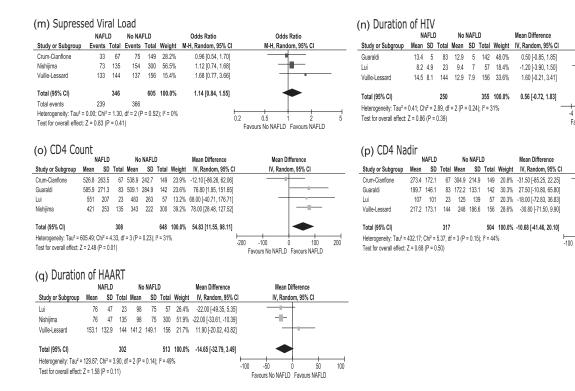
heavily weighted by one study defining significant fibrosis by transient elastography (liver stiffness  $\geq$ 7.1 kPa, n = 300) [18]. BMI (MD 1.38 95% CI 0.04–2.71 P = 0.04), fasting glucose [MD 0.80 (0.47–1.13) P < 0.00001] and AST level [MD 13.00 (4.34–21.65) P = 0.003] were associated with fibrosis, whereas male sex [OR 0.27 (0.15–0.51) P < 0.0001] and black ethnicity [OR 0.18 (0.08–0.44) P = 0.0002] were protective factors. CD4<sup>+</sup> cell count (NASH) and duration of HIV infection (fibrosis) were the only HIV-specific variables with data for meta-analysis, neither of which were associated with the outcome of interest (Fig. 4).

a) Age udy or Subgroup	NAFLD Mean SD T		IAFLD SD Total W		ean Difference /, Random, 95% Cl	Mean Difference IV, Random, 95% CI	(b) BMI Study or Subgr	NAFLD Dup Mean SD T		AFLD SD Total Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
um-Cianflone	40.1 10.2	67 39.3	1.5 149	15.4%	0.80 [-2.26, 3.86]		Crum-Cianflone	27.3 4	67 25.5	3.9 149 19.4%	1.80 [0.66, 2.94]	-1-
araldi	48.4 8.2 51.1 9			27.8% 6.3%	0.40 [-1.88, 2.68] -4.00 [-8.79, 0.79]		Guaraldi Lui	25.1 3.6 26.7 4.3	83 23 23 22.4	3.3 142 22.4% 3 57 11.0%	2.10 [1.15, 3.05] 4.30 [2.38, 6.22]	*
hijima		135 43		25.8%	0.00 [-2.37, 2.37]		Nishijima		135 21.8		3.20 [2.37, 4.03]	+
rling	47 9	9 42			5.00 [-6.29, 16.29]		Sterling	31 8.7		4.3 5 1.3%	4.00 [-2.82, 10.82]	
e-Lessard	49.6 9.5	144 49.3	12.3 156 :	23.6%	0.30 [-2.18, 2.78]	ſ	Vuille-Lessard	27.9 4.7	144 24.2	3.9 156 21.8%	3.70 [2.72, 4.68]	-
I (95% CI)		461	809 1	00.0%	0.11 [-1.09, 1.31]	•	Total (95% CI)		461	809 100.0%	2.92 [2.14, 3.70]	
	= 0.00; Chi <sup>2</sup> = 3.84 : Z = 0.18 (P = 0.8		.57); l² = 0%		-	20 -10 0 10 Favours No NAFLD Favours NAFLD		au <sup>2</sup> = 0.47; Chi <sup>2</sup> = 11 ffect: Z = 7.36 (P < 0		: 0.04); I <sup>2</sup> = 56%		-20 -10 0 10 20 Favours No NAFLD Favours NAFLD
,	rcumferen NAFLD Mean SD	No	NAFLD		Mean Difference IV, Random, 95% CI	Mean Difference IV. Random. 95% Cl	(d) Diabe Study or Subgr	NAFLD	No NAFI		Odds Ratio H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
um-Cianflone	96.2 11.9	67 87.9		35.3%	8.30 [5.02, 11.58]	IV, Kalidolii, 5376 Ci	Sterling		9 0	5	Not estimable	wert, Kandolit, 55% Of
araldi	90.3 9.2	83 83.9		46.2%	6.40 [3.90, 8.90]		Crum-Cianflone	4 6 19 14		149 9.7% 156 30.0%	1.29 [0.36, 4.56]	
	95.3 9.8	23 83.6			11.70 [6.41, 16.99]		Vuille-Lessard Nishijima	9 13		156 30.0% 300 20.2%	1.43 [0.70, 2.93] 1.58 [0.66, 3.78]	
							Guaraldi		3 16	142 26.5%	1.74 [0.81, 3.73]	±=
al (95% CI)		173	348	100.0%	8.05 [5.46, 10.64]	•	Lui	17 2	3 32	57 13.6%	2.21 [0.76, 6.44]	-
rogeneity: Tau <sup>2</sup>	= 2.14; Chi <sup>2</sup> = 3.3	86, df = 2 (P =	0.19); l² = 41%	0		-20 -10 0 10	20 Total (95% CI)	46		809 100.0%	1.61 [1.09, 2.39]	<b>•</b>
for overall effect	:t: Z = 6.10 (P < 0.	.00001)				Favours No NAFLD Favours NAFLD	) Heterogeneity: T	64 au <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0. ffect: Z = 2.38 (P = 0		: 0.96); I <sup>z</sup> = 0%	Ĕ	1.01 0.1 1 10 100 Favours No NAFLD Favours NAFLD
Hyperte	nsion NAFLD	No NAF		0	lds Ratio	Odds Ratio	(f) Triglyc					
y or Subgroup					Random, 95% Cl	M-H, Random, 95% Cl	Study or Subgrou	NAFLD Ip Mean SD T	No N otal Mean	AFLD SD Total Weight	Mean Difference IV, Random, 95% C	Mean Difference IV, Random, 95% CI
Cianflone	17 6	67 32	149 22.6%	6 1	1.24 [0.63, 2.44]		Crum-Cianflone	249.2 222.2	67 136.7	99.9 149 16.4%	112.50 [56.93, 168.07]	
		23 37	57 8.99		1.53 [0.52, 4.50]		Guaraldi	194 107.2 283.4 150.6	83 195.8 23 177.1 1	155 142 21.1% 06.3 57 13.9%	-1.80 [-36.18, 32.58] 106.30 [38.85, 173.75]	T
ma Lessard	36 13 32 14		300 43.3% 156 25.2%		1.82 [1.12, 2.96] 2.34 [1.23, 4.42]		Nishijima			118 300 22.6%	36.00 [8.72, 63.28]	
Lessalu	32 14	+4 17	100 20.27	°0 2	2.34 [1.23, 4.42]	-	Sterling	287 209	9 143	46 5 5.4%	144.00 [1.63, 286.37]	
(95% CI)	36		662 100.0%	% 1	1.75 [1.27, 2.41]	•	Vuille-Lessard	194.9 203.7	144 132.9	97.4 156 20.6%	62.00 [25.39, 98.61]	
events	102 = 0.00; Chi <sup>2</sup> = 1.	136	0.000 10 -	er.			Total (95% CI)		461	809 100.0%	61.52 [24.31, 98.74]	•
							Heterogeneity: Ta			- 0 002\· I2 = 74%		
for overall effect	ot: Z = 3.42 (P = 0	0.0006)	P	/0	Ö.I	01 0.1 1 10 Favours No NAFLD Favours NAFLD		r² = 1401.13; Chi² = 1: act: Z = 3.24 (P = 0.00		= 0.002); I <sup>2</sup> = 74%		-200 -100 0 100 200 Favours No NAFLD Favours NAFLD
for overall effect Choleste	erol NAFLD	No	IAFLD SD Total V	м	0.1 lean Difference /, Random, 95% Cl		Test for overall eff (h) HDL	act: Z = 3.24 (P = 0.00 NAFLD	1) No	NAFLD	Mean Difference t IV, Random, 95% C	Favours No NAFLD Favours NAFLD Mean Difference
Choleste or Subgroup Cianflone	erol NAFLD Mean SD T 190.7 47.7	No N	IAFLD SD Total M 39.2 149	M <u>Veight IV</u> 14.8%	lean Difference /, Random, 95% Cl 7.00 [-6.04, 20.04]	Favours No NAFLD Favours NAFLD Mean Difference	Test for overall eff (h) HDL <u>Study or Subgr</u> Crum-Clanflone	NAFLD NAFLD Nup Mean SD 35.7 10.1	1) No Fotal Mean 67 42.5	NAFLD <u>SD Total Weigh</u> 12.7 149 22.0%	t IV, Random, 95% C	Favours No NAFLD Favours NAFLD Mean Difference I IV, Random, 95%, Cl
Choleste or Subgroup Dianflone	erol NAFLD 190.7 47.7 194.9 47.6	No M otal Mean 67 183.7 83 199.5	IAFLD SD Total V 39.2 149 12.2 142	M <u>Veight IV</u> 14.8% 16.3% -	lean Difference /, Random, 95% CI 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77]	Favours No NAFLD Favours NAFLD Mean Difference	Test for overall eff (h) HDLCurry-Clanifore Guaraid	NAFLD NAFLD Maean SD - 35.7 10.1 42.9 13.9	1) <u>Fotal Mean</u> 67 42.5 83 46.8	NAFLD <u>SD Total Weigh</u> 12.7 149 22.0% 13.53 142 19.6%	t IV, Random, 95% C -6.80 [-9.96, -3.64] -3.90 [-7.63, -0.17]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI
Choleste or Subgroup Cianflone di	erol <u>Mean</u> SD T 190.7 47.7 194.9 47.6 197.2 34.8	No M otal Mean 67 183.7 3 83 199.5 4 23 181.7 3	IAFLD <u>SD Total W</u> 39.2 149 12.2 142 18.7 57	M Veight IV 14.8% 16.3% ~ 8.6% 1	ean Difference /, Random, 95% CI 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77] 5.50 [-1.91, 32.91]	Favours No NAFLD Favours NAFLD Mean Difference	(h) HDL (h) HDL Study or Subgr Crum-Ciantione Guardiai Lui	NAFLD Nup Mean SD 35.7 10.1 42.9 13.9 42.5 15.5	No <u>Fotal Mean</u> 67 42.5 83 46.8 23 46.4	NAFLD           SD         Total         Weigh           12.7         149         22.0%           13.53         142         19.6%           11.6         57         9.7%	<ul> <li>IV, Random, 95% C</li> <li>-6.80 [-9.96, -3.64]</li> <li>-3.90 [-7.63, -0.17]</li> <li>-3.90 [-10.91, 3.11]</li> </ul>	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl
Choleste or Subgroup Cianflone di na	erol <u>Mean</u> SD T 190.7 47.7 194.9 47.6 197.2 34.8	No M otal Mean 67 183.7 83 199.5 23 181.7 135 177	<b>IAFLD</b> <u>SD Total W</u> 19.2 149 12.2 142 18.7 57 40 300	M Veight IV 14.8% - 8.6% 1 29.1%	lean Difference /, Random, 95% CI 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77]	Favours No NAFLD Favours NAFLD Mean Difference	Test for overall eff (h) HDLCurry-Clanifore Guaraid	MAFLD           way         Mean         SD         *           100         Mean         SD         *         *           42.9         13.9         13.9         42.5         15.5         15         16         45         16         40         10         10	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39	SD         Total         Weigh           12.7         149         22.0%           13.53         142         19.6%           11.6         57         9.7%           16         300         21.6%           4.7         5         8.5%	IV, Random, 95% C           -6.80 [-9.96, -3.64]         -3.90 [-7.63, -0.17]           -3.90 [-7.63, -0.17]         -3.90 [-10.91, 3.11]           -1.00 [-4.25, 2.25]         1.00 [-6.72, 8.72]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI
Choleste or Subgroup Cianflone di na g	Erol NAFLD 190.7 47.7 194.9 47.6 197.2 34.8 183 45 183 37	No M otal Mean 67 183.7 83 199.5 23 181.7 135 177	<b>IAFLD</b> <u>SD Total W</u> 12.2 149 12.2 142 18.7 57 40 300 3 36 5	M Veight IV 14.8% 16.3% - 8.6% 1 29.1% 1.7% 3	ean Difference /, Random, 95% CI 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77] 5.50 [-1.91, 32.91] 6.00 [-2.84, 14.84]	Favours No NAFLD Favours NAFLD Mean Difference	test for overail eff (h) HDL (h) HDL (un-Ciantino Guaradai Lui Nishijima	MAFLD           way         Mean         SD         *           100         Mean         SD         *         *           42.9         13.9         13.9         42.5         15.5         15         16         45         16         40         10         10	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39	SD         Total         Weigh           12.7         149         22.0%           13.53         142         19.6%           11.6         57         9.7%           16         300         21.6%	IV, Random, 95% C           -6.80 [-9.96, -3.64]         -3.90 [-7.63, -0.17]           -3.90 [-7.63, -0.17]         -3.90 [-10.91, 3.11]           -1.00 [-4.25, 2.25]         1.00 [-6.72, 8.72]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl
Choleste or Subgroup Cianflone Idi ma g Lessard	MAFLD           Magan         SD         T           190.7         47.7         134.9         47.6           197.2         34.8         183         45           183         35         183.37         38.7	No M otal Mean 67 183.7 83 199.5 23 181.7 135 177 9 153	<b>IAFLD</b> <u>SD Total W</u> 12.2 149 12.2 142 18.7 57 40 300 3 36 5	M Veight IV 14.8% - 16.3% - 8.6% 1 29.1% - 1.7% 3 29.5% -	lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.60 [1-6.97, 7.77] 5.00 [1-91, 32.91] 6.00 [2.84, 14.84] 0.00 [9.75, 69.75] 7.80 [-0.97, 16.57]	Favours No NAFLD Favours NAFLD Mean Difference	(h) HDL <u>study or Subgr</u> Crum-Cannfone Guaraldi Lui Nishijima Sterring	MAFLD           way         Mean         SD         *           100         Mean         SD         *         *           42.9         13.9         13.9         42.5         15.5         15         16         45         16         40         10         10	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39	SD         Total         Weigh           12.7         149         22.0%           3.53         142         19.6%           11.6         57         9.7%           16         300         21.6%           4.7         5         8.5%	IV, Random, 95% C           -6.80 [-9.96, -3.64]         -3.90 [-7.63, -0.17]         -3.90 [-7.63, -0.17]         -3.90 [-10.91, 3.11]         -1.00 [-4.25, 2.25]         1.00 [-6.72, 8.72]         -7.70 [-11.65, -3.75]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI
Choleste or Subgroup Cianflone Ildi ma 19 Lessard (95% CI) ogeneity: Tau <sup>2</sup> =	MAFLD           Magan         SD         T           190.7         47.7         134.9         47.6           197.2         34.8         183         45           183         35         183.37         38.7	No No otal Mean 67 183.7 : 83 199.5 - 23 181.7 : 135 177 9 153 144 181.7 : 461 4, df = 5 (P = 0	AFLD           SD         Total         W           39.2         149         142           12.2         142         36.7         57           40         300         36         5           36.7         156         3           80.7         156         3	M Veight IV 14.8% - 16.3% - 8.6% 1 29.1% - 1.7% 3 29.5% -	lean Difference f, Random, 95% Cl 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77] 5.50 [-1.91] 32.91] 6.00 [-2.84, 14.84] 0.00 [-9.75, 69.75] 7.80 [-0.97, 16.57] 6.19 [0.93, 11.45]	Favours No NAFLD Favours NAFLD Mean Difference	(h) HDL Study or Subgrn Crum-Ciantione Guaratid Lui Nishijima Steriing Vuille-Lesari Heterogeneity: T Heterogeneity: T	MAFLD           way         Mean         SD         *           100         Mean         SD         *         *           42.9         13.9         13.9         42.5         15.5         15         16         45         16         40         10         10	1) Fotal Mean 67 42.5 83 46.8 23 46.4 135 46. 9 39 144 54.1 461 77, df = 5 (P =	SD         Total         Weigh           12.7         149         22.0%           13.53         142         19.6%           11.6         57         9.7%           16         300         21.6%           4.7         5         8.5%           19.3         156         18.7%           809         100.0%         100.0%	IV, Random, 95% C           -6.80 [-9.96, -3.64]         -3.90 [-7.63, -0.17]         -3.90 [-7.63, -0.17]         -3.90 [-10.91, 3.11]         -1.00 [-4.25, 2.25]         1.00 [-6.72, 8.72]         -7.70 [-11.65, -3.75]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI
Choleste or Subgroup -Cianflone aldi ima 19 -Lessard (95% CI) ogeneity: Tau <sup>2</sup> or overall effect	Mean         SD         T           190.7         47.7         194.9         47.6           191.7         34.8         197.2         34.8         197.2         34.8           183         35         183.3         35         183.3         189.5         38.7           = 4.41; ChP = 5.54         ChP = 5.54         ChP = 0.0         197.2         24.1         ChP = 0.0	No P Total Mean 67 183.7 : 83 199.5 - 23 181.7 : 135 177 9 153 144 181.7 : 461 4, df = 5 (P = 0 12)	Instant         Instant <thinstant< th=""> <thinstant< th=""> <thi< td=""><td>M Veight IV 14.8% - 16.3% - 8.6% 1 29.1% - 1.7% 3 29.5% -</td><td>lean Difference f, Random, 95% Cl 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77] 5.50 [-1.91] 32.91] 6.00 [-2.84, 14.84] 0.00 [-9.75, 69.75] 7.80 [-0.97, 16.57] 6.19 [0.93, 11.45]</td><td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl</td><td>(h) HDL Study or Subgr Caur-Clantlone Guardid Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity. T Test for overail e</td><td>weak         NAFLD           Weak         SD           36.7         10.1           42.5         13.9           42.5         15.5           45         16           46.4         15.5           10.4         4.6.4           15.5         2.3.16 (P=0.00000000000000000000000000000000000</td><td>1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39 144 54.1 461 77, df = 5 (P = 202)</td><td>VAFLD           SD         Total         Weigh           12.7         149         22.0%           3.53         142         196%           1.6         50         21.6%           4.7         5         8.5%           3.9         156         16.7%           809         100.0%         F = 55%</td><td>IV, Random, 95% C           -6.80 (19.96, 3.46)           -3.90 [-7.63, -0.17)           -3.90 [-10.91, 3.11]           -1.00 (1-22, 8.22)           .10.01 (-5.72, 8.72)           -7.70 [-11.85, -3.76]           -4.21 [-6.82, -1.59]</td><td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI</td></thi<></thinstant<></thinstant<>	M Veight IV 14.8% - 16.3% - 8.6% 1 29.1% - 1.7% 3 29.5% -	lean Difference f, Random, 95% Cl 7.00 [-6.04, 20.04] 4.60 [-16.97, 7.77] 5.50 [-1.91] 32.91] 6.00 [-2.84, 14.84] 0.00 [-9.75, 69.75] 7.80 [-0.97, 16.57] 6.19 [0.93, 11.45]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(h) HDL Study or Subgr Caur-Clantlone Guardid Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity. T Test for overail e	weak         NAFLD           Weak         SD           36.7         10.1           42.5         13.9           42.5         15.5           45         16           46.4         15.5           10.4         4.6.4           15.5         2.3.16 (P=0.00000000000000000000000000000000000	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39 144 54.1 461 77, df = 5 (P = 202)	VAFLD           SD         Total         Weigh           12.7         149         22.0%           3.53         142         196%           1.6         50         21.6%           4.7         5         8.5%           3.9         156         16.7%           809         100.0%         F = 55%	IV, Random, 95% C           -6.80 (19.96, 3.46)           -3.90 [-7.63, -0.17)           -3.90 [-10.91, 3.11]           -1.00 (1-22, 8.22)           .10.01 (-5.72, 8.72)           -7.70 [-11.85, -3.76]           -4.21 [-6.82, -1.59]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI
Choleste or Subgroup Dianfione di na essard essard 95% Cl) geneity: Tau <sup>2</sup> = r overall effect	Market         Market           Mean         SD         T           1907         47.7         194.9         47.6           1919.9         47.6         194.9         47.6           193         37         180.5         38.7           183         37         189.5         38.7           4.41:         Chi <sup>2</sup> = 5.54         Z         2.31 (P = 0.0           NAFLD         NAFLD         10.0         10.0	No N otal Mean 67 183.7 : 83 199.5 - 23 181.7 : 135 177 9 153 144 181.7 : 461 4, df = 5 (P = 0 12) No I	IAFLD         SD         Total         IV           39.2         149         142         142           12.2         142         36         5           40         300         3         36         5           80.7         156         3         369         1           335); I² = 10%         305; I² = 10%         10%         10%	M Veight IV 14.8% 16.3% 1 29.1% 1 29.5% 2 00.0%	lean Difference (, Random, 95% Cl 7.00 [6.04, 20.04] 4.60 [-16.97, 7.7] 5.50 [-1.91, 22.48, -14.84] 0.00 [-9.75, 69.75] 7.30 [-9.97, 16.57] 6.19 [0.93, 11.45] Lean Difference	Favours No NAFLD Favours NAFLD	(h) HDL (h) HDL Study or Subgr Crum-Canflone Guaraid Lui Nishijing Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall eff (j) Fastin	NAFLD           wear         52           35.7         10.1           42.5         13.5           42.5         15.5           45.7         16           40.10         10           46.4         15.5           8.62         5.46; ChiP = 11.1           Medic Z = 3.16 (P = 0.0)         0           G Glucose         NAFLD	1) Total Mean 67 42.5 83 46.8 48.3 46.8 9 39 144 54.1 461 77, df = 5 (P = 202) No M	VAFLD           SD         Total         Weigh           12.7         149         22.0%           3.33         142         196%           11.6         57         97%           16         300         21.6%           19.3         166         16.7%           19.3         166         16.7%           809         100.0%         0.05%           0.05); I* = 55%         AFLD	IV, Random, 95% C           -6.80 (1-9.6, -3.64)           -3.90 (7-8.3, -0.17)           -3.90 [7-8.3, -0.17)           -3.90 [-10.91, -3.11]           -1.00 (1-27, 2.872)           1.00 [-6.72, 8.72]           -7.70 [-11.65, -3.75]           -4.21 [-6.82, -1.59]           Mean Difference	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI IV, Random, 95% C
Choleste or Subgroup Zianfione di assessard sessard 35% CI) geneity: Tau <sup>2</sup> = r overall effect coverall effect	Mean         SD         T           190.7         47.7         194.9         47.6           197.2         34.8         37         195.5         38.7           183         45.5         38.7         2.31 (P = 0.0         2.31 (P = 0.0           NAFLD           MAFLD         MAFLD         MAFLD	No N Cotal Mean 67 183.7 : 83 199.5 - 23 181.7 : 135 177 9 153 144 181.7 : 461 k, df = 5 (P = 0 12) No 1 Total Mean	AFLD SD Total V 39.2 149 12.2 142 140 300 3 36 5 38.7 156 3 809 1 35); I <sup>2</sup> = 10% VAFLD SD Total V	M Veight IV 14.8% 16.3% - 29.1% 1 29.1% 1 1.7% 3 29.5% 00.0% M Weight IV	Iean Difference /, Random, 95% CI 7.00 [6.04, 20.04] 4.80 [1-6.97, 7.48] 5.50 [1-91, 32.91] 6.00 [2.24, 14.84] 0.00 [2-36, 14.84] 6.19 [0.93, 11.45] Ean Difference /, Random, 95% CI	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(h) HDL study or Subgr Crum-Cannfone Guarraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall eff (j) Fastin Study or Subgr	wet Z = 3.24 (P = 0.00           Wean SD           35.7 10.1           42.9 139           42.5 15.5           45           16           w2 = 5.46; ChiP = 1.1           % Glucose           NAFLD	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46.4 9 39 144 54.1 461 17, df = 5 (P = No N Total Mean	NAFLD         SD         Total         Weight           127         149         220%         333         142         166         300         21.6%           116         50         21.6%         31         16         18.7%         809         100.0%         0.05%         F = 55%           AFLD           SD         Total         Weight	t IV, Random, 95% ( - 6.80 [-9.6, -3.6] - 3.90 [-7.8, -0.17] - 3.90 [-10.91, -3.17] - 3.90 [-10.91, -3.17] - 1.00 [4.25, 2.25] - 7.70 [-11.65, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI Grand Stress Favours No NAFLD Favours NAFLD Mean Difference
Choleste or Subgroup Janflone di as essard 55% CI) overall effect DL or Subgroup Dianflone	Mean         SD         T           1907         47.7         190.7         47.7           1907         47.7         194.9         47.6           197.2         34.8         133         45           183         37         189.5         38.7           2         2.31 (P = 0.0         2.2         2.31 (P = 0.0           NAFLD           Mean         SD         1           113.1         39         127.6         38.7	No N otal Mean 67 183.7 : 83 199.5 - 23 181.7 : 135 177 9 153 144 181.7 : 461 4, df = 5 (P = 0 12) No I	AFLD         SD         Total         W           \$9.2         149         122         142           \$8.7         57         36         5           \$8.7         156         :         809         1           36         5         :         809         1           35); I <sup>2</sup> = 10%         :         :         :         :           VAFLD         :         :         :         :         :           33         :	M         M           Veight         IV           14.8%         -           16.3%         -           29.1%         1           29.1%         -           29.1%         -           00.0%         0           Veight         IV           Veight         IV           Veight         IV           Veight         IV	lean Difference (, Random, 95% Cl 7.00 [6.04, 20.04] 4.60 [-16.97, 7.7] 5.50 [-1.91, 22.48, -14.84] 0.00 [-9.75, 69.75] 7.30 [-9.97, 16.57] 6.19 [0.93, 11.45] Lean Difference	Favours No NAFLD Favours NAFLD	(h) HDL Study or Subgr Crum-Cantone Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi	wetz         = 3.24 (P = 0.00           Wean         SD           400         Mean           500         7           101         4.29           42.5         15.5           45         16           40.1         10.4           45.5         16           40.1         10.4           45.5         15.5           40.1         10.4           46.4         15.5           40.1         10.4           46.4         15.5           40.1         10.4           46.4         15.5           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1         10.4           40.1	1) Total Mean 67 42.5 83 46.4 135 46.4 135 46.4 9 39 144 54.1 461 7, df = 5 (P = ) 002) No N Total Mean 83 5.4	SD         Total         Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           809         100,0%         000,5%           AFLD         SD         Total         Weight           15         142         23,5%	t IV, Random, 95% C -6.80 [9.96, 3.46] -3.90 [7.83, 0.17] -3.90 [1.03, 0.17] -3.90 [1.03, 1.17] -1.00 [4.25, 2.25] 1.00 [6.72, 8.72] -7.70 [-11.65, -3.75] -4.21 [6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [0.11, 0.91]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI Graduate State -20 -10 0 10 2 Favours No NAFLD Favours NAFLD Mean Difference
Choleste or Subgroup iianflone ii a essard 55% Cl) terneity: Tau <sup>2</sup> = overall effect DL DL or Subgroup iianflone di	Mean         SD         T           190.7         47.7         194.9         47.6           194.9         47.6         194.9         47.6           195.2         34.8         37         183.3           183         45         38.7         189.5         38.7           = 4.41: ChiP = 5.54         Z         2.31 (P = 0.0         113.1         39           112.6         38.7         112.1         38.7         122.6         38.7	No h           Total Mean         67 183.7 :           83 199.5 - 3:         31 181.7 :           135 177 9 153         144 181.7 :           461         461           8, df = 5 (P = 0 12)         120           No 1           Total Mean           67 114.2         83 127.6           32 107.6         23 100.7	IAFLD           SD         Total         W           92.2         149         142           12.2         142         142           38.7         57         36           36         5         38.7           38.7         156         3           33.35); I <sup>2</sup> = 10%         10%           VAFLD         Total         V           33         149         34.8         142           30.9         57         142         30.9         57	M         Veight         V           14.8%         -         -           16.3%         -         -           29.1%         -         -           1.7%         3         -           29.5%         -         -           00.0%         -         -           Veight         1         -           12.4%         -         -           14.0%         C         -	lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.80 [-16.97, 7.48] 5.50 [-1.91, 32.91] 6.00 [2.84, 14.84] 0.00 [-3.75, 89] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] Hean Difference (, Random, 95% CI -1.10 [-11.84, 9.64] 2.00 [-10.10, 10.10] 2.01 [-10.10, 10.13]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI	(h) HDL <u>study or Subgr</u> Court-Clantione Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% Cl) Heterogeneity. T Test for overall e (j) Fastin <u>Study or Subgr</u> Guaraldi Lui	$\label{eq:rescaled_rescale} \begin{array}{c} \textbf{NAFLD}\\ \textbf{Wean} & \textbf{SD} \\ \hline \textbf{Wean} & \textbf{SD} \\ \hline \textbf{Mean} & \textbf{SD} \\ \textbf{Mean} & \textbf{SD} \\ \textbf{Mean} \\ Mea$	1) Total Mean 67 42.5 83 46.8 23 46.4 9 39 144 54.1 461 70, df = 5 (P = 202) No M Total Mean 83 5.4 23 6.1	SD         Total         Weight           127         149         20,0%           13,53         142         196,9%           16         50         21,6%           19,3         156         18,7%           19,3         156         18,7%           00,005); P = 55%         55%           SD           SD           50         7144           9,57         4,8%	IV, Random, 95% C           -6.80 (9.96, 3.36)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -1.00 (4.25, 2.22)           -7.70 [-11.85, -3.76]           -4.21 [-6.82, -1.59]           Wean Difference           IV, Random, 95% C           0.40 [-0.11, 0.91]           1.00 [-0.13, 2.13]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI Graduate State -20 -10 0 10 2 Favours No NAFLD Favours NAFLD Mean Difference
Choleste or Subgroup Jianflone di essard or Subgroup DL or Subgroup Dianflone di na a	Mean         SD         T           190.7         47.7         194.9         47.6           197.2         34.8         183         37           183.4         5         38.7         189.5           4.41: Chi <sup>2</sup> = 5.54         2.2.31 (P = 0.0         127.6         38.7           113.1         39         127.6         38.7         112.7         38.7           112.1         32.7         32.7         32.7         33.7         112.1         39.7           112.1         38.7         112.7         38.7         112.7         38.7           112.3         39.7         127.6         38.7         112.7         38.7	No h           67         183.7           33         199.5           23         181.7           135         177           9         153           144         181.7           461         , off = 5 (P = 0           92)         184.7           67         114.2           83         127.6           83         127.6           135         103.9           9         8	SD         Total         W           99.2         149         142           12.2         142         142           88.7         57         57           36         5         5           80.7         156         3           35); I <sup>2</sup> = 10%         33         149           44.8         142         30.9         57           29         300         20         57	M         Veight         IV         V </td <td>lean Difference /, Random, 95% C1 7.00 [6.04, 20.04] 4.60 [1-6.97, 7.40 [6.47, 7.40] 5.50 [1-91, 32.01] 6.00 [2.43, 14.43] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [1-13.4, 9.64] 1.10 [1-13.4, 9.64] 1.10 [1-13.4, 9.64] 1.00 [1-13.4, 9.63] 8.00 [2.11, 13.89] 8.00 [2.11, 13.89]</td> <td>Favours No NAFLD Favours NAFLD</td> <td>(h) HDL Study or Subgr Crum-Clamfone Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard</td> <td>Mean         SD           40         Mean         SD           425         155         45           40         140         429         139           425         155         16         40         10           464         155         16         40         10           464         155         16         16         10           9         GUCOSe         NAFLD         NAFLD         10         10           000         Mean         SD         58         2.1         7.1         2.5         5.8         1.3</td> <td>1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39 24 45.4 144 54.1 461 07, df = 5 (P = 1000) No N Stal Mean 83 5.4 23 6.1 144 5.4</td> <td>NAFLD         SD         Total         Weight           12.7         149         22.0%         33.142         196.4%           11.6         57         9.7%         16         30.0         21.6%           11.6         57         9.7%         16         30.0         21.6%           19.3         156         18.7%         809         100.0%         0.05%         17.5%         55%           AFLD         SD         Total         Weight         15.         142         23.5%         19.3         156         71.7%</td> <td>t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.85, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI Grand Stress Favours No NAFLD Favours NAFLD Mean Difference</td>	lean Difference /, Random, 95% C1 7.00 [6.04, 20.04] 4.60 [1-6.97, 7.40 [6.47, 7.40] 5.50 [1-91, 32.01] 6.00 [2.43, 14.43] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [1-13.4, 9.64] 1.10 [1-13.4, 9.64] 1.10 [1-13.4, 9.64] 1.00 [1-13.4, 9.63] 8.00 [2.11, 13.89] 8.00 [2.11, 13.89]	Favours No NAFLD Favours NAFLD	(h) HDL Study or Subgr Crum-Clamfone Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard	Mean         SD           40         Mean         SD           425         155         45           40         140         429         139           425         155         16         40         10           464         155         16         40         10           464         155         16         16         10           9         GUCOSe         NAFLD         NAFLD         10         10           000         Mean         SD         58         2.1         7.1         2.5         5.8         1.3	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46 9 39 24 45.4 144 54.1 461 07, df = 5 (P = 1000) No N Stal Mean 83 5.4 23 6.1 144 5.4	NAFLD         SD         Total         Weight           12.7         149         22.0%         33.142         196.4%           11.6         57         9.7%         16         30.0         21.6%           11.6         57         9.7%         16         30.0         21.6%           19.3         156         18.7%         809         100.0%         0.05%         17.5%         55%           AFLD         SD         Total         Weight         15.         142         23.5%         19.3         156         71.7%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.85, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI Grand Stress Favours No NAFLD Favours NAFLD Mean Difference
Choleste or subgroup Jianfione di essard 35% CI) geneity: Tau <sup>2</sup> s 0 overall effect <b>DL</b> or Subgroup Cianfione di na	Mean         SD         T           Mean         SD         T           190.7         47.7         194.9         47.6           197.2         34.8         183         37           180.5         38.7         189.5         38.7           4.41:         Chi = 5.54         2.2         2.31 (P = 0.0           Mean         SD         1         12.0         38.7           113.1         39         127.6         38.7         12.1         38.7	No h           67         183.7           33         199.5           23         181.7           135         177           9         153           144         181.7           461         , off = 5 (P = 0           92)         184.7           67         114.2           83         127.6           83         127.6           135         103.9           9         8	SD         Total         W           99.2         149         142           12.2         142         142           88.7         57         57           36         5         5           80.7         156         3           35); I <sup>2</sup> = 10%         33         149           44.8         142         30.9         57           29         300         20         57	M         Veight         IV         V </td <td>lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.60 [16.97, 7.77] 6.00 [2.84, 14.84] 0.00 [4.76, 827] 7.80 [-0.97, 16.57] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-11.84, 9.64] 0.00 [-10.10, 10.10] 11.60 [6.13, 29.33]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI</td> <td>(h) HDL Study or Subgr Crum-Cantine Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI)</td> <td>ware         5.48         2.11           200         Mean         SD           300         3.29         3.21           301         3.29         3.25           302         3.25         3.55           303         3.25         3.55           304         3.55         3.55           305         3.60         2.51           304         3.55         1.65           304         1.05         3.66           305         G         G         G           305         G         G         G         G           306         Mean         SD         1         1           307         S8         2.11         7.1         2.5           5.8         1.3         3         3</td> <td>1) Total Mean 67 42.5 83 46.8 23 46.4 135 46.9 9 39 144 54.1 461 7, df = 5 (P = 1) Total Mean 83 5.4 23 6.1 144 5.4 23 6.1 144 5.4</td> <td>NAFLD           SD Total Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         23.5%           AFLD           SD Total Weight           15         142         23.5%           13         156         71.7%         355           355         100.0%         13         156         71.7%</td> <td>IV, Random, 95% C           -6.80 (9.96, 3.36)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -1.00 (4.25, 2.22)           -7.70 [-11.85, -3.76]           -4.21 [-6.82, -1.59]           Wean Difference           IV, Random, 95% C           0.40 [-0.11, 0.91]           1.00 [-0.13, 2.13]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI Grand Stress Favours No NAFLD Favours NAFLD Mean Difference</td>	lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.60 [16.97, 7.77] 6.00 [2.84, 14.84] 0.00 [4.76, 827] 7.80 [-0.97, 16.57] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-11.84, 9.64] 0.00 [-10.10, 10.10] 11.60 [6.13, 29.33]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI	(h) HDL Study or Subgr Crum-Cantine Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI)	ware         5.48         2.11           200         Mean         SD           300         3.29         3.21           301         3.29         3.25           302         3.25         3.55           303         3.25         3.55           304         3.55         3.55           305         3.60         2.51           304         3.55         1.65           304         1.05         3.66           305         G         G         G           305         G         G         G         G           306         Mean         SD         1         1           307         S8         2.11         7.1         2.5           5.8         1.3         3         3	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46.9 9 39 144 54.1 461 7, df = 5 (P = 1) Total Mean 83 5.4 23 6.1 144 5.4 23 6.1 144 5.4	NAFLD           SD Total Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         23.5%           AFLD           SD Total Weight           15         142         23.5%           13         156         71.7%         355           355         100.0%         13         156         71.7%	IV, Random, 95% C           -6.80 (9.96, 3.36)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -3.90 (7.83, -0.17)           -1.00 (4.25, 2.22)           -7.70 [-11.85, -3.76]           -4.21 [-6.82, -1.59]           Wean Difference           IV, Random, 95% C           0.40 [-0.11, 0.91]           1.00 [-0.13, 2.13]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95%, CI Grand Stress Favours No NAFLD Favours NAFLD Mean Difference
Choleste or Subgroup Cianflone di na g. essard 95% C1) genetiy: Tau <sup>2</sup> = r overall effect DL or Subgroup Cianflone ldi ma g. Lessard (g5% C1) genetiy: Tau <sup>2</sup>	Mean         SD         T           1907         47.7         190.7         47.7           1907         47.7         192.9         47.6           197.2         34.8         37         189.5         38.7           180.5         38.7         2         2.31 (P = 0.0         0           Mean         SD         1         113.1         39           127.6         38.7         127.6         38.7           112.1         38.7         127.6         38.7           112.1         38.7         122.7         32.1           12.1         30.9         91         32           112.1         30.9         12.1         30.9	No N           Cotal Mean           67           83           135           135           141           153           144           161           , cf = 5 (P = 0)           23           120	SD         Total         V           \$82         149         9           \$22         142         8           \$87         57         30           \$40         300         156           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         14           \$33         149         3           \$44         12         300         20           \$20         5         3         3           \$20         5         3         4           \$20         5         3         4           \$20         5         5         3	M         IV           Veight         IV           14.8%         8.6%           8.6%         1           29.1%         3           29.5%         3           12.4%         -           12.4%         -           12.4%         -           12.4%         -           12.4%         -           25.9%         -	lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [-1.91, 32.21] 6.00 [2.43, 14.64] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.138, 9.33] 8.00 [2.11, 1.389] 3.00 [2.12, 28, 33.28] 7.70 [2.66, 15.14] 5.80 [2.01, 9.58]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl 	(h) HDL Study or Subgr Crum-Clantione Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) FaStin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T	Mean         SD           40         Mean         SD           425         155         45           40         140         429         139           425         155         16         40         10           464         155         16         40         10           464         155         16         16         10           9         GUCOSe         NAFLD         NAFLD         10         10           000         Mean         SD         58         2.1         7.1         2.5         5.8         1.3	1) <u>Fotal Mean</u> 67 42.5 83 46.8 23 46.4 135 46 9 39 144 54.1 <b>461</b> 17, df = 5 (P = 1000) <b>No N</b> <u>Fotal Mean</u> 83 5.4 23 6.1 144 5.4 23 0.1 144 5.4	NAFLD           SD Total Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         23.5%           AFLD           SD Total Weight           15         142         23.5%           13         156         71.7%         355           355         100.0%         13         156         71.7%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.85, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI IV, Random, 95% C
Choleste or Subgroup. Clanfone Idi ma g. Lessard (g5% Cl) genetiy: Tau <sup>2</sup> = or overall effect LDL cor Subgroup. Clanfone add ma g. Lessard (g5% Cl) genetiy: Tau <sup>2</sup>	Mean         SD         T           Mean         SD         T           190.7         47.7         194.9         47.6           197.2         34.8         183         37           180.5         38.7         189.5         38.7           =4.41; ChP = 5.54         2.2         2.31 (P = 0.0           Mean         SD         1         129           91         22         38.7         112.1         38.7           91         32         112.1         30.9         91         32           91.21.1         30.9         91         32         112.1         30.9           =0.00; ChP = 4.05	No M           Cotal Mean         67         183.7         181.7         1135         117.7         1135         117.7         1135         117.7         1141         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         1461         135         103         114         127.6         23         100.5         135         103         9         85         127.6         23         100.5         135         103         9         85         144         104.4         461 <td>SD         Total         V           \$82         149         9           \$22         142         8           \$87         57         30           \$40         300         156           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         14           \$33         149         3           \$44         12         300         20           \$20         5         3         3           \$20         5         3         4           \$20         5         3         4           \$20         5         5         3</td> <td>M         IV           Veight         IV           14.8%         8.6%           8.6%         1           29.1%         3           29.5%         3           12.4%         -           12.4%         -           12.4%         -           12.4%         -           12.4%         -           25.9%         -</td> <td>lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [-1.91, 32.21] 6.00 [2.43, 14.64] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.138, 9.33] 8.00 [2.11, 1.389] 3.00 [2.12, 28, 33.28] 7.70 [2.66, 15.14] 5.80 [2.01, 9.58]</td> <td>Favours No NAFLD Favours NAFLD</td> <td>(h) HDL Study or Subgr Crum-Clantione Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) FaStin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T</td> <td><math display="block">\label{eq:rescaled_rescale} \begin{array}{c} \textbf{NAFLD}\\ \textbf{Wear SD}\\ \hline \textbf{Wear SD}\\ \hline \textbf{Merr}\\ </math></td> <td>1) <u>Fotal Mean</u> 67 42.5 83 46.8 23 46.4 135 46 9 39 144 54.1 <b>461</b> 17, df = 5 (P = 1000) <b>No N</b> <u>Fotal Mean</u> 83 5.4 23 6.1 144 5.4 23 0.1 144 5.4</td> <td>NAFLD           SD Total Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         23.5%           AFLD           SD Total Weight           15         142         23.5%           13         156         71.7%         355           355         100.0%         355         100.0%</td> <td>t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.85, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference V, Random, 95% Cl -20 -10 0 10 20 Favours No NAFLD Favours NAFLD Mean Difference V, Random, 95% Cl</td>	SD         Total         V           \$82         149         9           \$22         142         8           \$87         57         30           \$40         300         156           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         3           \$809         1         14           \$33         149         3           \$44         12         300         20           \$20         5         3         3           \$20         5         3         4           \$20         5         3         4           \$20         5         5         3	M         IV           Veight         IV           14.8%         8.6%           8.6%         1           29.1%         3           29.5%         3           12.4%         -           12.4%         -           12.4%         -           12.4%         -           12.4%         -           25.9%         -	lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [-1.91, 32.21] 6.00 [2.43, 14.64] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.138, 9.33] 8.00 [2.11, 1.389] 3.00 [2.12, 28, 33.28] 7.70 [2.66, 15.14] 5.80 [2.01, 9.58]	Favours No NAFLD Favours NAFLD	(h) HDL Study or Subgr Crum-Clantione Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) FaStin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T	$\label{eq:rescaled_rescale} \begin{array}{c} \textbf{NAFLD}\\ \textbf{Wear SD}\\ \hline \textbf{Wear SD}\\ \hline \textbf{Merr}\\ $	1) <u>Fotal Mean</u> 67 42.5 83 46.8 23 46.4 135 46 9 39 144 54.1 <b>461</b> 17, df = 5 (P = 1000) <b>No N</b> <u>Fotal Mean</u> 83 5.4 23 6.1 144 5.4 23 0.1 144 5.4	NAFLD           SD Total Weight           127         149         22,0%           133         142         196%           11.6         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         23.5%           AFLD           SD Total Weight           15         142         23.5%           13         156         71.7%         355           355         100.0%         355         100.0%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.85, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69]	Favours No NAFLD Favours NAFLD Mean Difference V, Random, 95% Cl -20 -10 0 10 20 Favours No NAFLD Favours NAFLD Mean Difference V, Random, 95% Cl
Choleste or subgroup Clanflone Idi ma (95% C1) genetiy: Tau <sup>2</sup> a or overall effect LDL Clanflone Idi ma 1g -Lessard (95% C1) orgenetiy: Tau <sup>2</sup> or or overall effect	Mean         SD         T           Mean         SD         T           190.7         47.7         194.9         47.6           197.2         34.8         183         37           180.5         38.7         189.5         38.7           =4.41; ChP = 5.54         2.2         2.31 (P = 0.0           Mean         SD         1         129           91         22         38.7         112.1         38.7           91         32         112.1         30.9         91         32           91.21.1         30.9         91         32         112.1         30.9           =0.00; ChP = 4.05	No M           Cotal Mean         67         183.7         181.7         1135         117.7         1135         117.7         1135         117.7         1141         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         1461         135         103         114         127.6         23         100.5         135         103         9         85         127.6         23         100.5         135         103         9         85         144         104.4         461 <td>SD         Total         V           SD         Total         V           382.7         142         38.7         57           40         300         156         3           88.7         156         3         36         5           809         1         3         35;); 1° = 10%         10%           VAFLD           SD         Total         V           33         149         34.8         142           30.9         57         29         300         20         5           34.8         156         809         1         5           809         1         5         5         4.8         156           809         1         5         5         4.8         156</td> <td>M         Veight         IV           14.8%         1         1           16.3%         1         2           17%         3         2           29.1%         1         1           1.7%         3         0           00.0%         0         1           Veight         1         2           1.24%         -         -           1.24%         -         1           25.9%         1         3           25.9%         2         5</td> <td>lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [-1.91, 32.21] 6.00 [2.43, 14.64] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.138, 9.33] 8.00 [2.11, 1.389] 3.00 [2.12, 28, 33.28] 7.70 [2.66, 15.14] 5.80 [2.01, 9.58]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl</td> <td>(i) AST (b) HDL Study or Subgr Cour-Cainfone Guaraldi Lui Nishijima Stering Vuile-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuile-Lessard (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Test for overall e (j) AST</td> <td>vect Z = 3.24 (P = 0.000           vect Z = 3.24 (P = 0.000           vect Z = 3.24 (P = 0.000           vect Z = 3.24 (P = 0.000           35.7 10.1           42.9 13.9           42.5 15.5           45.5 15.6           40           40.10           46.4 15.5           38.7 2.3.16 (P = 0.000           vect Z = 3.16 (P = 0.000           vect Z = 3.37 (P = C           vect Z = 3.37 (P = C</td> <td>1) Total Mean 67 42.5 83 46.8 23 46.4 9 39 144 54.1 461 7, df = 5 (P = No N Total Mean 83 5.4 23 6.1 144 5.4 250 12, df = 2 (P = 0,007)</td> <td>VAFLD           SD         Total         Weight           127         149         220%           13.3         142         19%           16         300         216%           17.5         8.5%         160.0%           19.3         156         18.7%           809         100.0%         0.0%           0.00.0%         F = 55%         42           AFLD         5         142         23.5%           19.3         156         71.7%         355           10.00%         0.60); P = 0%         355         100.0%           0.60); P = 0%         VAFLD         VAFLD         10.0%</td> <td>t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.77] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -1.17] - 7.70 [-1.16, -3.75] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [0.11, 0.01] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.68] 0.43 [0.18, 0.68] Mean Difference</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20</td>	SD         Total         V           SD         Total         V           382.7         142         38.7         57           40         300         156         3           88.7         156         3         36         5           809         1         3         35;); 1° = 10%         10%           VAFLD           SD         Total         V           33         149         34.8         142           30.9         57         29         300         20         5           34.8         156         809         1         5           809         1         5         5         4.8         156           809         1         5         5         4.8         156	M         Veight         IV           14.8%         1         1           16.3%         1         2           17%         3         2           29.1%         1         1           1.7%         3         0           00.0%         0         1           Veight         1         2           1.24%         -         -           1.24%         -         1           25.9%         1         3           25.9%         2         5	lean Difference /, Random, 95% Cl 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [-1.91, 32.21] 6.00 [2.43, 14.64] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.184, 9.64] 1.10 [-1.138, 9.33] 8.00 [2.11, 1.389] 3.00 [2.12, 28, 33.28] 7.70 [2.66, 15.14] 5.80 [2.01, 9.58]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(i) AST (b) HDL Study or Subgr Cour-Cainfone Guaraldi Lui Nishijima Stering Vuile-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Total (95% CI) Heterogeneity: T Study or Subgr Guaraldi Lui Vuile-Lessard (j) Fastin Study or Subgr Guaraldi Lui Vuile-Lessard Test for overall e (j) AST	vect Z = 3.24 (P = 0.000           35.7 10.1           42.9 13.9           42.5 15.5           45.5 15.6           40           40.10           46.4 15.5           38.7 2.3.16 (P = 0.000           vect Z = 3.16 (P = 0.000           vect Z = 3.37 (P = C	1) Total Mean 67 42.5 83 46.8 23 46.4 9 39 144 54.1 461 7, df = 5 (P = No N Total Mean 83 5.4 23 6.1 144 5.4 250 12, df = 2 (P = 0,007)	VAFLD           SD         Total         Weight           127         149         220%           13.3         142         19%           16         300         216%           17.5         8.5%         160.0%           19.3         156         18.7%           809         100.0%         0.0%           0.00.0%         F = 55%         42           AFLD         5         142         23.5%           19.3         156         71.7%         355           10.00%         0.60); P = 0%         355         100.0%           0.60); P = 0%         VAFLD         VAFLD         10.0%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.77] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -1.17] - 7.70 [-1.16, -3.75] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [0.11, 0.01] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.68] 0.43 [0.18, 0.68] Mean Difference	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup. Clanfone Idi ma g. Lessard (85% Cl) (95% Cl) genetiy: Tau <sup>2</sup> = or overall effect LDL cor Subgroup eLessard (95% Cl) ogenetiy: Tau <sup>2</sup> (95% Cl) ogenetiy: Tau <sup>2</sup> or overall effect ALT or Subgroup	Mean         SD         T           1907         47.7         190.7         47.7           1907         47.7         190.7         47.6           1912         34.8         183         37           1805         38.7         189.5         38.7           2.2         2.31 (P = 0.0         197.2         38.7           121.1         2.2         2.31 (P = 0.0         11.2           127.6         38.7         11.2         39.9           9         12         112.1         30.9         11.2           9         9         32         112.1         30.9         12.2         3.00 (P = 0.0           L Z = 3.00 (C hP = 4.00         L Z = 3.00 (P = 0.0)	No N           Otal Mean           67 183.71           33 199.5           23 181.7           135 177           9 153           144 181.7           461           , df = 5 (P = 0)           20)           No I           67 114.2           33 127.6           23 100.5           135 100.5           135 100.3           9 85           144 104.4           461           5, df = 5 (P = 0)           003)           No N           No N N	AFLD         SD         Total         W           39.2         149         142         142           12.2         142         36         5           38.7         57         56         5           38.7         156         5         3           38.7         156         5         3           35); I² = 10%         3         3         149           33         149         30.9         57           34.8         156         809         1           534.8         156         809         1           5.54); I² = 0%         8         4         4           AFLD         8         4         156           809         1         5         1.54); I² = 0%	M         Weight         IV           14.8%         -         -           16.3%         -         -           17.9%         3         -           29.1%         -         -           1.7%         3         -           29.1%         -         -           Veight         14         -           1.4.0%         0         -           1.4.0%         -         -           1.9%         6         -           25.9%         -         -           00.0%         -         -           eight         V         -	ean Difference /, Random, 95% CI 7.00 [6.04, 20.04] 4.00 [1-8.97, 7.03 5.50 [1-91, 32.21] 6.00 [2.48, 14.64] 6.09 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 4.10 [-11.84, 9.64] 1.10 [-11.84, 9.64] 1.10 [-11.84, 9.64] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl 400 50 Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl 400 50 50 50 Favours No NAFLD Favours NAFLD 50 50 50 50 50 50 50 50 50 50	(h) HDL Study or Subgr Crum-Clamfone Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) AST Study or Subgr	wet Z = 3.24 (P = 0.00           wet X = 3.24 (P = 0.00           Mean SD           36.7 10.1           42.9 139           42.5 15.5           45 16           40 10           46.4 15.5           36.7 10.1           29 39           au <sup>2</sup> = 5.46; Chill = 11,1           filed: Z = 3.16 (P = 0.0)           buy         Mean SD           5.8 2.1           7.1 2.5           5.8 1.3           au <sup>3</sup> = 0.00; Chill = 1,1           field: Z = 3.37 (P = C           buy         Mean SD           5.8 2.1           7.1 2.5           5.8 1.3           au <sup>3</sup> = 0.00; Chill = 1,1           field: Z = 3.37 (P = C           buy         MAFLD	1) Total Mean 67 42.5 83 48.8 23 46.4 135 46.9 9 39 144 54.1 461 77, df = 5 (P = 1000) Total Mean 83 54 23 6.1 144 5.4 250 12, df = 2 (P = 1000) 12, df = 2 (P = 1000) 13, df = 1000 (P = 1000) 14, d	NAFLD         SD         Total         Weight           127         149         220%         333         142         168         333         142         168         333         142         168         187         7         5         857         19.3         156         18.7%         809         100.0%         0.05); IF = 55%         50         50         7         7.8%         19.3         156         16.1%         19.1%         13.1         156         71.7%         355         100.0%         355         100.0%         0.60); IF = 0%         VAFLD         SD         SD         Total         Weight         SD         7.7%         355         100.0%	t IV, Random, 95% C - 6.80 [-9.6, -3.6] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -1.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [-0.11, 0.51] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.68] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C	Favours No NAFLD Favours NAFLD Mean Difference N, Random, 95% CI -20 -30 Favours NAFLD Favours NAFLD Mean Difference N, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Clanfone Idi ma g Lessard (95% Cl) geneity: Tau <sup>2</sup> = or overall effect Clanflone Idi ma ig Lessard (95% Cl) geneity: Tau <sup>2</sup> cr overall effect ALT or Subgroup	Mean         SD         T           1907         47.7         190.9         47.6           1919.9         47.6         191.9         41.8           183         37         189.5         38.7           184.9         4.61         CP         2.2           2.2         2.31 (P = 0.0         100.0         100.0           Mean         SD         1         1.3         39           127.6         38.7         112.7         38.7           112.1         38.7         112.7         39.9           9         32         112.1         30.9         9         32.12           112.1         30.9         9         1.2         3.00 (P = 0.0         0.00         Chi <sup>2</sup> = 4.02           L2         3.00 (P = 0.0         Chi <sup>2</sup> = 4.02         1.2         1.30.9         1.2         1.2	No h           67         183.7           83         199.5           23         181.7           135         177           9         153           144         181.7           461         (ff = 5 (P = 0))           12)         No 1           Fotal Mean         67           67         114.2           83         127.6           23         100.5           135         103           9         85           144         104.4           461         5, df = 5 (P = 0)           9         85           144         104.4           461         5, df = 5 (P = 0)           9         85           144         104.4           461         003)           No N         328.4	SD         Total         V           SD         Total         V           38.7         57         36         5           40         300         ::         809         1           38.7         156         :         809         1           38.7         156         :         809         1           33         51; 1° = 10%         .         .         .           VAFLD         SD         Total         V         .           33         143         142         .         .         .           30.9         57         .         .         .         .         .           20         5         .         .         .         .         .         .         .           .54); 1° = 0%         .	Multiple         Multiple           Veight         V           11         11           11         13%           11         13%           12         13%           12         13%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           14         12%           100.0%         14%           11         14%           12         14%           14         14%           100.0%         14%           100.0%         14%	Lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.80 [1-63, 7.24] 5.50 [1-91, 32.91] 6.00 [2.24, 14.84] 0.00 [9.75, 897] 6.19 [0.93, 11.45] 6.19 [0.93, 1	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(h) HDL Study or Subgr Crum-Cantifue Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) AST Study or Subgr Guaraldi	WaFLD         MaFLD           up         Mean         SD           457         101         429           425         155         45           425         155         45           40         10         464           457         131         464           458         21         71           459         132         155           45         16         40           464         155         155           58         2.1         7.1           58         2.1         7.1         2.5           58         1.3         3.3         2.2         3.32           49         0.00; Chi <sup>2</sup> = 1.3         7.1         2.5           58         1.3         3.32         2.22         2.2	1) Total Mean 67 42.5 83 46.8 135 46.9 9 39 144 54.1 461 77, df = 5 (P = 1000) 144 54.1 461 83 5.4 23 6.1 144 5.4 23 6.1 144 5.4 250 22, df = 2 (P = 1000) No No Total Mean 83 25.1	NAFLD           SD Total Weight           116         57         97%           16         300         216%           19.3         156         18.7%           809         100.0%         20.5%           AFLD           SD Total Weight           13         156         71.7%           355         100.0%         0.60); F = 0%           VAFLD           Weight           355         100.0%           0.60); F = 0%         S55	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] 0.40 [-0.11, 0.91] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C 6.10 [2.94, 13.26]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Cianflone di na g Lessard 95% C1) geneity: Tau <sup>2</sup> = or overall effect Cianflone did ma gg Lessard (g5% C1) ggeneity: Tau <sup>2</sup> = cr overall effect ALT or Subgroup di	Mean         SD         T           Mean         SD         T           1907. 47.7         194.9         47.6           1972. 234.8         183.37         189.5           183.4         37         189.5         38.7           2.4.11. ChP = 5.54         Z. = 2.31 (P = 0.0         0           Mean         SD         T           113.1         39         127.6         38.7           112.1         30.9         91         32           112.1         30.9         91         32           12.1.1         30.9         91         32           0.00: ChP = 4.00:         LZ = 3.00 (P = 0.0         0           MAFLD         MAFLD         MAFLD           4.43         39         13         35	No N           Total Mean         67         183.7         31         199.5         23         181.7         1135         117.7         1135         117.7         1135         117.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1145         1145         1135         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         114         104.4         461         144         104.4         461         154.6         114         104.4         114         114         114         114         114         114         114         114         114         114         114         114         1144         1144         1144	AFLD         SD         Total         W           52         142         142         142           52         142         36         5           36         5         36         5           809         1         33         149           335); I* = 10%         33         149           33         149         30,9         57           29         300         20         5           34.8         156         142           15.54); I* = 0%         809         1           50         Total         W           6.3         142         2           8.09         1         50           8.09         1         50           8.09         1         50	M         W           14.8%         1           16.3%         1           29.5%         2           29.5%         1           12.4%         -           12.4%         -           12.4%         -           12.4%         -           12.4%         -           00.0%         -           41.2%         -           5.9%         -           44.6%         2           5.9%         -	Lean Difference (, Random, 95% C1 7.00 [-6.04, 20.04] 4.60 [-16.07, 777] 5.50 [-1.91, 32.91] 6.00 [-2.84, 14.84] 0.00 [-3.75, 897] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(h) HDL Study or Subgr Crum-Clamfone Guaraldi Lui Nishijma Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) AST Study or Subgr	wet Z = 3.24 (P = 0.00           wet X = 3.24 (P = 0.00           Mean SD           36.7 10.1           42.9 139           42.5 15.5           45 16           40 10           46.4 15.5           36.7 10.1           29 39           au <sup>2</sup> = 5.46; Chill = 11,1           filed: Z = 3.16 (P = 0.0)           buy         Mean SD           5.8 2.1           7.1 2.5           5.8 1.3           au <sup>3</sup> = 0.00; Chill = 1,1           field: Z = 3.37 (P = C           buy         Mean SD           5.8 2.1           7.1 2.5           5.8 1.3           au <sup>3</sup> = 0.00; Chill = 1,1           field: Z = 3.37 (P = C           buy         MAFLD	1) Total Mean 67 42.5 83 48.8 23 46.4 135 46.9 9 39 144 54.1 461 77, df = 5 (P = 1000) Total Mean 83 54 23 6.1 144 5.4 250 12, df = 2 (P = 1000) 12, df = 2 (P = 1000) 13, df = 1000 (P = 1000) 14, d	NAFLD         SD         Total         Weight           127         149         220%         333         142         168         333         142         168         333         142         168         187         7         5         857         19.3         156         18.7%         809         100.0%         0.05); IF = 55%         50         50         7         7.8%         19.3         156         16.1%         19.1%         13.1         156         71.7%         355         100.0%         355         100.0%         0.60); IF = 0%         VAFLD         SD         SD         Total         Weight         SD         7.7%         355         100.0%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.63, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -1.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] Mean Difference IV, Random, 95% C 0.40 [0.11, 0.61] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C 8.10 [2.94, 13.26]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Cianflone di na g Lessard 95% CI) geneity: Tau <sup>2</sup> r overall effect Cianflone g Lessard g Lessard (di r overall effect or overall effect or overall effect no overall effect or overall effect at a subgroup di na	Mean         SD         T           1907         47.7.         190.7         47.7.           1919.2         34.8         191.2         34.8           183         37         1805.5         38.7           1805         38.7         2         2.31 (P = 0.0           Mean         SD 1         112.1         38.7           113.1         38.7         12.6         38.7           112.1         38.7         112.1         38.7           112.6         38.7         112.1         39.9           91         32         112.1         30.9           2.0.00 (ChP = 0.00)         ChP = 0.00         ChP = 0.00           MAFLD         MART         12.6         38.7           112.1         30.9         9         32         112.1           30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00	No N           Total Mean         67         183.7         31         199.5         23         181.7         1135         117.7         1135         117.7         1135         117.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1144         181.7         1145         1145         1135         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         113         114         104.4         461         144         104.4         461         154.6         114         104.4         114         114         114         114         114         114         114         114         114         114         114         114         1144         1144         1144	SD         Total         V           SD         Total         V           99.2         149         142           187.57         57         156           809         1         36           807         156         3           809         1         35); I* = 10%           AFELD           SD         Total           33         149         34.8           30.9         57         29         300           20         57         34.8         156         36.9           809         1         56.         809         1           5.54); I* = 0%         8         8         156           SD         Total         W           6.3         142         21           8.54); I* = 0%         57         1         18           57         1         18         57         1           20         200         11         18         57         1           20         20         20         20         20         1	Mill         Mill           Veight         IV           116.3%         -           129.1%         -           29.1%         -           29.1%         -           117%         3           29.5%         -           00.0%         -           Veight         IV           4.5%         1           4.2%         -           25.9%         -           00.0%         -           4.5%         1           25.9%         -           00.0%         -           4.5%         1           5.9%         -           5.9%         -           5.9%         -	Lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.80 [1-63, 7.24] 5.50 [1-91, 32.91] 6.00 [2.24, 14.84] 0.00 [9.75, 897] 6.19 [0.93, 11.45] 6.19 [0.93, 1	Favours No NAFLD Favours NAFLD  Mean Difference IV, Random, 95% CI  Mean Difference IV, Random, 95% CI	(h) HDL Study or Subgr Crum-Clantine Guaraldi Lui Nishijima Stefring Vulle-Lessard Total (95% Cl) Heterogeneity: T Test for overall e (j) FaStin Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Test for overall e (j) AST Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Test for overall e (l) AST Study or Subgr Guaraldi Lui Nishijima	vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi <sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000	1) Total Mean 67 42.5 83 46.4 135 46.9 9 39 144 54.1 461 7, df = 5 (P = 1000) 144 54.1 461 135 46.4 135 46.4 144 54.1 144	SD Total Weigh           SD         Total         Weigh           127         149         220%           33         142         166%         20%           116         57         97%           16         300         216%           19.3         156         18.7%           809         100.0%         25.5%           SD Total         Weight           15         142         23.5%           19.3         156         71.7%           355         100.0%         F= 0%           VAFLD           VAFLD           11.8         142         25.6%           12.1%         12.4%         12.4%           13         156         71.7%           355         100.0%         F           11.8         142         25.1%           12.4%         30         12.4%           7         5         0.12.4%           7         5         7	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] - 4.21	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Cianfone Idi ma g Lessard sys% CI) geneity: Tau <sup>2</sup> = or overall effect LDL or Subgroup Cianfone Idi ma geneity: Tau <sup>2</sup> ussard (95% CI) ogeneity: Tau <sup>2</sup> or overall effect MLT or Subgroup Idi	Mean         SD         T           1907         47.7.         190.7         47.7.           1919.2         34.8         191.2         34.8           183         37         1805.5         38.7           1805         38.7         2         2.31 (P = 0.0           Mean         SD 1         112.1         38.7           113.1         38.7         12.6         38.7           112.1         38.7         112.1         38.7           112.6         38.7         112.1         39.9           91         32         112.1         30.9           2.0.00 (ChP = 0.00)         ChP = 0.00         ChP = 0.00           MAFLD         MART         12.6         38.7           112.1         30.9         9         32         112.1           30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00           MART         30.00 (P = 0.00)         ChP = 0.00         ChP = 0.00	No N           Total Mean         67         183.7         3         181.7         13         181.7         13         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         144         181.7         12         167         1142         161         162.7         12         127.6         23         100.5         12         100.5         12         127.6         23         100.5         135         103         9         85         144         104.4         461         5, df = 5 (P = 0         0003)         9         85         144         104.4         461         3         28.4         144         123         27         135         43         24.4         123         27         135         43         9         67	SD         Total         Y           \$32.2         149         142           \$32.2         142         36         5           \$40.300         36         5         38.7         156         3           \$80.7         156         3         809         1         33         149         33         149           \$33.5         1°         20         5         30.9         57         30.9         57         30.9         57         34.8         156         809         1         5.54); ° = 0%         809         1         5.54); ° = 0%         809         1         5.54); ° = 0%         809         1         20         5         3.42         20         5         3.42         20         5         3.42         3.55); ° = 0%         8.54); ° = 0%         8.54); ° = 0%         8.54); ° = 0%         8.53)         142         2.0         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142         3.3         142 <td>M         W           Veight         IV           11         11           11         13           11         13           11         13           11         13           11         13           12         14           14.0%         0           00.0%         14           14.0%         1           14.0%         25.9%           00.0%         14           15.0%         25.9%           00.0%         14           15.5%         2           15.5%         2           14.4%         10</td> <td>lean Difference /, Random, 95% CI 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [1-91, 32.21] 6.00 [2.43, 14.64] 0.00 [-3.75, 69.75] 7.80 [0.93, 11.45] 6.19 [0.93, 11.45] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58]</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl</td> <td>(h) HDL Study or Subgr Crum-Clanifone Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (i) AST Study or Subgr Guaraldi Lui Nishijima</td> <td>vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi<sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000</td> <td>1) Total Mean 67 42.5 83 46.4 135 46.9 9 39 144 54.1 461 7, df = 5 (P = 144 54.1 461 135 46.4 135 46.9 9 39 144 54.1 461 23 46.4 135 46.9 135 54 23 6.1 144 5.4 250 12, df = 2 (P = No N No N N No N N N N N N N N N N N N N N</td> <td>SD         Total         Weight           127         149         220%           116         57         97%           116         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         0.05%           SD         Total         Weight           1.5         142         23.5%           0.60%         7         4.8%           3.35         100.0%         0.60%           0.60%         7         7.7%           355         100.0%         25%           VAFLD         S         Total           SD         Total         Weight           1.3         156         71.7%           355         100.0%         25%           VAFLD         S         17.7%           S         156         71.7%</td> <td>t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] - 4.21</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20</td>	M         W           Veight         IV           11         11           11         13           11         13           11         13           11         13           11         13           12         14           14.0%         0           00.0%         14           14.0%         1           14.0%         25.9%           00.0%         14           15.0%         25.9%           00.0%         14           15.5%         2           15.5%         2           14.4%         10	lean Difference /, Random, 95% CI 7.00 [6.04, 20.04] 4.00 [1-6.97, 7.03 5.50 [1-91, 32.21] 6.00 [2.43, 14.64] 0.00 [-3.75, 69.75] 7.80 [0.93, 11.45] 6.19 [0.93, 11.45] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58] 5.80 [2.01, 9.58]	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% Cl	(h) HDL Study or Subgr Crum-Clanifone Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (j) Fastin (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall ef (i) AST Study or Subgr Guaraldi Lui Nishijima	vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi <sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000	1) Total Mean 67 42.5 83 46.4 135 46.9 9 39 144 54.1 461 7, df = 5 (P = 144 54.1 461 135 46.4 135 46.9 9 39 144 54.1 461 23 46.4 135 46.9 135 54 23 6.1 144 5.4 250 12, df = 2 (P = No N No N N No N N N N N N N N N N N N N N	SD         Total         Weight           127         149         220%           116         57         97%           116         57         97%           19.3         156         18.7%           19.3         156         18.7%           809         100.0%         0.05%           SD         Total         Weight           1.5         142         23.5%           0.60%         7         4.8%           3.35         100.0%         0.60%           0.60%         7         7.7%           355         100.0%         25%           VAFLD         S         Total           SD         Total         Weight           1.3         156         71.7%           355         100.0%         25%           VAFLD         S         17.7%           S         156         71.7%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 3.90 [-1.93, -0.17] - 1.00 [4.25, 2.25] - 7.70 [-1.16, -3.75] - 4.21 [-6.82, -1.59] - 4.21	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Clanflone di gestandone gs% C1) genetity: Tau <sup>2</sup> a or overall effect <b>DL</b> <b>Clanflone</b> did ma igg Lessard (g5% C1) or overall effect or overall effect <b>ALT</b> or Subgroup di ma gelessard	Mean         SD         T           1907         47.5         199.9         47.6           1919.2         34.8         37         189.5         38.7           183         45         183         37         189.5         38.7           24.41         ChiP = 5.54         22         2.31 (P = 0.0         100.0         113.1         39         127.6         38.7         112.1         38.7         112.1         38.7         112.1         39.7         112.1         39.9         12         12.2         30.0         (P = 0.0         112.1         39.9         12         12.2         3.00         (P = 0.0         112.1         39.7         12.1         39.9         12         12.2         3.00         (P = 0.0         112.1         30.9         112.1         32.9         112.1         30.9         112.1         32.9         112.1         30.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9	No P           67         183.7           33         199.5           23         181.7           135         177           9         153           144         181.7           461         (f = 5 (P = 0))           12)         19           144         181.7           451         (f = 5 (P = 0))           120         10.5           135         107.3           53         127.6           35         103.5           144         104.4           461         5, df = 5 (P = 0)           5, df = 5 (P = 0)         003)           003)         85           144         104.4           461         104.4           451         123           27         135           135         32           32         27           135         33           9         67           144         28.7	SD         Total         V           SD         Total         V           382.7         142         38.7         57           40         300         156         3           88.7         57         156         3           809         1         3         157           33.51; I* = 10%         VAFLD         VAFLD         VAFLD           33.48         142         30.9         57           20         5         34.8         156           809         1         5.54); I* = 0%         809           AFLD         809         1         5.54); I* = 0%           AFLD         20         5         14.2         2           9.0         30.1         2.7         15         14.2           9.2         30.0         1         2.7         15           9.2         30.0         1         2.7         15           9.2         30.0         1         2.7         1           6.3         142         2         3         142         2           9.2         300         1         6         5         4.2	M         V           Veight         IV           11         11           11         13%           12         13%           12         13%           12         13%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           12         14%           14         14%           14         14%           14         14%           14         14%           14         14%           14         14%           14         14%           14         14%           14         14%	Lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.60 [1-63, 7.14] 5.50 [1-19], 32.01] 6.00 [2.44, 14.84] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.10 [0.13, 26, 15.14] 5.80 [2.01, 9.58] 7.70 [0.26, 13.26] 2.80 [11.13, 34.7] 6.00 [0.61, 32.61] 2.20 [5.03, 38, 20] 2.20 [5.20, 38, 20] 2.20 [5.20, 38, 20] 2.20 [5.20, 38,	Favours No NAFLD Favours NAFLD  Mean Difference IV, Random, 95% CI  Mean Difference IV, Random, 95% CI	(h) HDL Study or Subgr Crum-Clantifice Guaraldi Lui Nishijima Stering Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (j) Fastin Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e (i) AST Study or Subgr Guaraldi Lui Vuille-Lessard Total (95% CI) Heterogeneity: T Test for overall e Study or Subgr Guaraldi Lui Nishijima Sterling Vuille-Lessard Study or Subgr	vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi <sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000	1) Total Mean 67 42.5 83 46.8 23 46.4 135 46.9 9 39 144 54.1 461 137, df = 5 (P = 1000) Total Mean 83 5.4 23 6.1 144 5.4 250 12, df = 2 (P = 1000) Total Mean 83 25.1 23 27 135 34 9 56 144 27.3	SD Total Weigh           SD         Total         Weigh           127         149         220%           33         142         166%         20%           116         57         97%           16         300         216%           19.3         156         18.7%           809         100.0%         25.5%           SD Total         Weight           15         142         23.5%           19.3         156         71.7%           355         100.0%         F= 0%           VAFLD           VAFLD           11.8         142         25.6%           12.1%         12.4%         12.4%           13         156         71.7%           355         100.0%         F           11.8         142         25.1%           12.4%         30         12.4%           7         5         0.12.4%           7         5         7	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 4.21 [-6.82, -1.59] 0.40 [-0.11, 0.51] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C 8.10 [2.94, 13.26] 6.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.51, 13.26] - 7.00 [-3.8, 14.38] - 7.00 [-3.8, 14	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20
Choleste or Subgroup Cianfone di ma g Lessard (95% C1) (95% C1) or Subgroup con Subgroup (2) (2) (2) (2) (2) (2) (3) (3) (3) (3) (4) (4) (4) (4) (4) (4) (4) (4	Mean         SD         T           1907         47.5         199.9         47.6           1919.2         34.8         37         189.5         38.7           183         45         183         37         189.5         38.7           24.41         ChiP = 5.54         22         2.31 (P = 0.0         100.0         113.1         39         127.6         38.7         112.1         38.7         112.1         38.7         112.1         39.7         112.1         39.9         12         12.2         30.0         (P = 0.0         112.1         39.9         12         12.2         3.00         (P = 0.0         112.1         39.7         12.1         39.9         12         12.2         3.00         (P = 0.0         112.1         30.9         112.1         32.9         112.1         30.9         112.1         32.9         112.1         30.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9         112.1         32.9	No N           Total Mean         67         183.7         3           33         199.5         23         181.7         1           135         177         9         153         144         181.7         1           144         181.7         1         461         1         14.2         181.7         2         100.5           6.7         114.2         181.7         3         461         1         14.2         13.5         103         2         100.5         135         103         9         85         144         104.4         461         145.5         144         104.4         461         5.0         135         103         9         85         144         104.4         461         83         28.4         12.3         27         135         43         29         67         132         27         135         43         29         67         144         28.7         1         39         67         144         28.7         1         39         67         144         28.7         1         39         67         144         28.7         1         39         67         144         28.7         1 <td>SD         Total         W           \$92         149         142           \$12.2         142         36         5           \$12.2         142         36         5           \$88.7         156         3         36         5           \$87         57         156         3         36         5           \$809         1         35); I* = 10%         33         149         33         149           \$33         149         30.0         20         5         34.8         156         300         20         5         34.8         156         16         5         4         156         142         30.0         20         5         34.8         156         16         5         34.8         156         16         5         3         142         30.0         1         35; I* 2         20         5         34.8         156         16         17         19         30.0         1         35; I* 1         16         14         18         37         1         35         142         2         18         57         1         36         5         14         36         5         14         &lt;</td> <td>M         Veight         IV           Veight         IV         Veight         IV           16.3%         -         -         -           29.1%         -         -         -           29.1%         -         -         -           29.1%         -         -         -           29.5%         -         -         -           00.0%         -         -         -           Veight         IV         -         -           12.4%         -         -         -           00.0%         -         -         -           4.5%         1         -         -           00.0%         -         -         -           4.5%         -         -         -           5.9%         -         -         -           00.0%         -         -         -         -           4.5%         -         -         -         -           5.5%         2         -         -         -           1.4%         42.0         -         -         -</td> <td>Lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.60 [1-6.97, 7.03 5.50 [1-91, 32.21] 6.00 [2.43, 14.43] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.10 [0.13, 20.33] 7.70 [0.26, 15.14] 5.80 [2.01, 9.58] 7.80 [2.01, 3.34.7] 6.00 [0.61, 32.61] 2.20 [5.03, 38, 20] 0.[27, 24, 44, 108, 44] 9.00 [3.75, 14.25] 5.88 [8.04, 23.92]</td> <td>Favours No NAFLD Favours NAFLD  Mean Difference IV, Random, 95% CI  Mean Difference IV, Random, 95% CI</td> <td>(h) HDL Study or Subgr Courr-Clarifone Guaraldi Lui Nishijima Stering Vulle-Lessard Total (95% Cl) 100 (j) Fastin (j) Fastin Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Test for overall e (j) AST Study or Subgr Guaraldi Lui Vulle-Lessard (j) Fastin Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Study or Subgr Guaraldi Lui Nishijima Stering Vulle-Lessard Total (95% Cl)</td> <td>vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi<sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000</td> <td>1) Total Mean 67 42.5 83 46.4 135 46.9 9 39 144 54.1 461 77, df = 5 (P = 144 54.1 461 83 5.4 23 6.1 144 5.4 23 6.1 144 5.4 250 122, df = 2 (P = No N Total Mean 83 25.1 23 27 135 34 9 56 144 27.3 394</td> <td>VAFLD           SD Total Weight 15:16         57           16:30         2:6%         4:7         5         8:5%           19:3         156         16:0         9:7%         9:7%           19:3         156         16:0         9:7%         9:00.9%           0:005);         F = 55%         5:0         100.0%         100.0%           SD Total Weight           15         142         2:3.5%         0:0.0%           0:80;         F = 0%         3:55         100.0%         0:0.0%           0:80;         F = 0%         3:55         100.0%         12:4%           11:8         142         2:5.5%         3:55         100.0%           0:80);         F = 0%         3:55         100.0%         12:4%           3:5         7:5         0:3.5%         3:55         10:7%           4:11:8         142         2:50.5%         3:5%         3:5%           8:4         156         5:0.5%         3:5%         3:5%</td> <td>t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 4.21 [-6.82, -1.59] 0.40 [-0.11, 0.51] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C 8.10 [2.94, 13.26] 6.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.51, 13.26] - 7.00 [-3.8, 14.38] - 7.00 [-3.8, 14</td> <td>Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20</td>	SD         Total         W           \$92         149         142           \$12.2         142         36         5           \$12.2         142         36         5           \$88.7         156         3         36         5           \$87         57         156         3         36         5           \$809         1         35); I* = 10%         33         149         33         149           \$33         149         30.0         20         5         34.8         156         300         20         5         34.8         156         16         5         4         156         142         30.0         20         5         34.8         156         16         5         34.8         156         16         5         3         142         30.0         1         35; I* 2         20         5         34.8         156         16         17         19         30.0         1         35; I* 1         16         14         18         37         1         35         142         2         18         57         1         36         5         14         36         5         14         <	M         Veight         IV           Veight         IV         Veight         IV           16.3%         -         -         -           29.1%         -         -         -           29.1%         -         -         -           29.1%         -         -         -           29.5%         -         -         -           00.0%         -         -         -           Veight         IV         -         -           12.4%         -         -         -           00.0%         -         -         -           4.5%         1         -         -           00.0%         -         -         -           4.5%         -         -         -           5.9%         -         -         -           00.0%         -         -         -         -           4.5%         -         -         -         -           5.5%         2         -         -         -           1.4%         42.0         -         -         -	Lean Difference (, Random, 95% CI 7.00 [6.04, 20.04] 4.60 [1-6.97, 7.03 5.50 [1-91, 32.21] 6.00 [2.43, 14.43] 6.19 [0.93, 11.45] 6.19 [0.93, 11.45] 6.10 [0.13, 20.33] 7.70 [0.26, 15.14] 5.80 [2.01, 9.58] 7.80 [2.01, 3.34.7] 6.00 [0.61, 32.61] 2.20 [5.03, 38, 20] 0.[27, 24, 44, 108, 44] 9.00 [3.75, 14.25] 5.88 [8.04, 23.92]	Favours No NAFLD Favours NAFLD  Mean Difference IV, Random, 95% CI  Mean Difference IV, Random, 95% CI	(h) HDL Study or Subgr Courr-Clarifone Guaraldi Lui Nishijima Stering Vulle-Lessard Total (95% Cl) 100 (j) Fastin (j) Fastin Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Test for overall e (j) AST Study or Subgr Guaraldi Lui Vulle-Lessard (j) Fastin Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Study or Subgr Guaraldi Lui Vulle-Lessard Total (95% Cl) Heterogeneity: T Study or Subgr Guaraldi Lui Nishijima Stering Vulle-Lessard Total (95% Cl)	vect Z = 3.24 (P = 0.000           vect Z = 3.57 (D = 1.0000           vect Z = 3.46 (Chi <sup>2</sup> = 1.11)           vect Z = 3.47 (P = 0.00000)           vect Z = 3.37 (P = 0.0000000000000000000000000000000000	1) Total Mean 67 42.5 83 46.4 135 46.9 9 39 144 54.1 461 77, df = 5 (P = 144 54.1 461 83 5.4 23 6.1 144 5.4 23 6.1 144 5.4 250 122, df = 2 (P = No N Total Mean 83 25.1 23 27 135 34 9 56 144 27.3 394	VAFLD           SD Total Weight 15:16         57           16:30         2:6%         4:7         5         8:5%           19:3         156         16:0         9:7%         9:7%           19:3         156         16:0         9:7%         9:00.9%           0:005);         F = 55%         5:0         100.0%         100.0%           SD Total Weight           15         142         2:3.5%         0:0.0%           0:80;         F = 0%         3:55         100.0%         0:0.0%           0:80;         F = 0%         3:55         100.0%         12:4%           11:8         142         2:5.5%         3:55         100.0%           0:80);         F = 0%         3:55         100.0%         12:4%           3:5         7:5         0:3.5%         3:55         10:7%           4:11:8         142         2:50.5%         3:5%         3:5%           8:4         156         5:0.5%         3:5%         3:5%	t IV, Random, 95% C - 6.80 [-9.6, 3.64] - 3.90 [-7.8, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 3.90 [-1.03, -0.17] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 7.70 [-1.18, -3.75] - 4.21 [-6.82, -1.59] 0.40 [-0.11, 0.51] 1.00 [-0.13, 2.13] 0.40 [0.11, 0.69] 0.43 [0.18, 0.68] Mean Difference IV, Random, 95% C 8.10 [2.94, 13.26] 6.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.58, 13.83] 31.00 [-1.51, 13.26] - 7.00 [-3.8, 14.38] - 7.00 [-3.8, 14	Favours No NAFLD Favours NAFLD Mean Difference IV, Random, 95% CI -20 -20 -20 -20 -20 -20 -20 -20

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

**Fig. 3. Forest plots for nonalcoholic fatty liver disease risk factors.** (a) Age, (b) BMI, (c) waist circumference, (d) diabetes, (e) hypertension, (f) triglycerides, (g) total cholesterol, (h) HDL, (i) LDL, (j) fasting glucose, (k) ALT, (l) AST, (m) suppressed viral load, (n) duration of HIV infection, (o) CD4<sup>+</sup> cell count, (p) CD4<sup>+</sup> nadir, (q) duration of HAART. The diagnosis of diabetes and hypertension were based on the concomitant use of medications for these conditions. ALT, alanine aminotransferase; AST,

aspartate aminotransferase.



#### Fig. 3. (Continued)

There was significant statistical heterogeneity for age  $(I^2 = 85\% P = 0.0002)$ .

# Discussion

The current study provides the first systematic review of the literature with meta-analysis examining the prevalence and risk factors of NAFLD, NASH and fibrosis in HIV-monoinfected patients.

Ten studies met criteria for inclusion in the review. We carefully excluded studies that were confounded with HCV infection or high alcohol intake, for example [9,24], and the small number of studies enrolled in our review highlights that NAFLD in HIV-monoinfection has been a long-neglected field of research.

Based on radiological criteria, our review found a prevalence of NAFLD in HIV-monoinfected of 35%. Prevalence estimates in the general population vary significantly with diagnostic modality and study population. A recent systematic review has reported a worldwide prevalence of NAFLD diagnosed by imaging at 25%. Stratified by region, the prevalence in Asia, Europe and the United States America was 27, 24 and 24%, respectively [4]. However, the figure increases up to 70% in diabetic patients and over 90% among obese patients [25].

Only one study has directly compared the prevalence of liver steatosis between HIV and non-HIV patients [9]. The study showed a lower prevalence in HIV patients at 13 vs. 19% (P = 0.02) in non-HIV patients, but the study included 9% of patients with positive HCV antibodies that may have influenced these results (genotype 3 is a recognized cause of steatosis).

Mean Difference

IV. Random. 95% CI

Favours No NAFLD Favours NAFLD

Mean Difference

IV, Random, 95% CI

Favours No NAFLD Favours NAFLD

100

-50

In contrast to this, our data suggest that the prevalence of NAFLD in HIV-monoinfected patients may be higher (35%) than the general population (25%). Our metaanalysis confirms that parameters of the metabolic syndrome are significantly associated with the development of NAFLD in HIV as observed in the general population. Significantly, higher CD4<sup>+</sup> cell count was also associated with NAFLD, whereas duration of HIV infection or HAART, HIV viral load and CD4<sup>+</sup> cell count nadir were not. This suggests that well treated HIV patients might be at higher risk of NAFLD, although interestingly age and HAART exposure were not associated.

There were insufficient data to meta-analyse exposure by drug class. Only the study by Guaraldi *et al.* [21] identified cumulative nucleoside reverse transcriptase inhibitors exposure to be associated with NAFLD. This was in a population with a median exposure of 124 months, and given the time period this may have included hepatotoxic 'D-drugs' (didanosine, zalcitabine and stavudine), although this is not specified in the article. Four other

(a) Age				(b) Male Ge	nder						
(0) / 90	Fibrosis No Fibrosis	Mean Difference	Mean Difference		Fibrosis	No Fibrosis		Odds Ratio	Odds		
Study or Subgroup Crum-Cianflone	Mean         SD         Total         Mean         SD         Total         Weight           57         5.7         2         40.3         10.5         53         20.8%	IV, Random, 95% Cl 16.70 [8.31, 25.09]	IV, Random, 95% Cl	Study or Subgroup Crum-Cianflone	Events Tota 2 2			V, Random, 95% Cl 0.24 [0.01, 6.52] +	IV, Randor	n, 95% Cl	
Ingiliz Morse	41.5 6.5 6 48.2 8.8 24 24.1% 53 6 12 48 10 47 26.9%	-6.70 [-12.98, -0.42] 5.00 [0.56, 9.44]		Ingiliz Morse	6 6 11 12			0.83 [0.03, 22.87] + 0.75 [0.07, 7.92]			
Vuille-Lessard	53.2 11 45 49.2 10.9 255 28.2%	4.00 [0.52, 7.48]		Vuille-Lessard	23 45			0.24 [0.12, 0.47]			
Total (95% CI)	65 379 100.0% = 39.19; Chi <sup>2</sup> = 20.11, df = 3 (P = 0.0002); I <sup>2</sup> = 85%	4.32 [-2.45, 11.09]		Total (95% CI)	65	379	100.0%	0.27 [0.15, 0.51]	•		
Test for overall effect		-2 Fav	0 -10 0 10 20 ours No Fibrosis Favours Fibrosis	Total events Heterogeneity: Tau <sup>2</sup> =	42 0.00: Chi <sup>2</sup> = 1.2	325 7. df = 3 (P = 0.74	4);  ² = 0%	-		<u>!</u>	<u> </u>
				Test for overall effect:			,,	1	0.05 0.2 1 Favours No Fibrosis	5 Favours Fibrosis	20
(c) BMI											
	Fibrosis No Fibrosis	Mean Difference	Mean Difference	(d) Fasting (							
Study or Subgroup Crum-Cianflone	Mean         SD         Total         Mean         SD         Total         Weight           29.7         2.3         2         27.8         4.4         53         12.7%	IV, Random, 95% Cl 1.90 [-1.50, 5.30]	IV, Random, 95% Cl	Study or Subgroup	Fibrosis Mean SD To	No Fibrosis tal Mean SD	s Total Weight	Mean Difference IV, Random, 95% CI	Mean Di IV, Rando		
Ingiliz Morse	23 1.6 6 23 3.4 24 30.0%	0.00 [-1.87, 1.87]		Crum-Cianflone Ingiliz	6.9 3.9 5.54 1.23	2 5.3 1.2 6 5.08 0.54	53 0.4% 24 11.0%				-
Vuille-Lessard	29 3 12 28 5 47 24.1% 28.7 5.5 45 26 4.7 255 33.2%	1.00 [-1.22, 3.22] 2.70 [0.99, 4.41]		Morse Vuille-Lessard	6.28 0.83	12 5.51 0.72	47 42.3% 255 46.3%	0.77 [0.26, 1.28]		* *	
Total (95% CI)	65 379 100.0%	1.38 [0.04, 2.71]	•			40 0.0 1.2 65	379 100.0%				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	= 0.64; Chi <sup>2</sup> = 4.59, df = 3 (P = 0.20); l <sup>2</sup> = 35% - 7 = 2.02 (P = 0.04)	-10	-5 0 5 10	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0	.00; Chi <sup>2</sup> = 0.69,	df = 3 (P = 0.87); H		0.80 [0.47, 1.13]	-10 -5 (	▼ ) 5	10
	. 2 2.02 () 0.01)	Fav	ours No Fibrosis Favours Fibrosis	Test for overall effect: Z	= 4.70 (P < 0.00	001)			Favours No Fibrosis		
(a) Trialuca	ridoc			(f) Cholester	rol						
(e) Triglyce	Fibrosis No Fibrosis	Mean Difference	Mean Difference	.,	Fibrosis	No Fibros		Mean Difference		ifference	
Study or Subgroup	Mean SD Total Mean SD Total Weigi	nt IV, Random, 95% Cl	IV, Random, 95% Cl	Study or Subgroup Crum-Cianflone	Mean SD To 238 48.1	tal Mean SD 2 187.2 47.3	Total Weigh		I IV, Rand	om, 95% Cl	
Crum-Cianflone Ingiliz	368.5 208.6 2 177.1 95.7 53 8.4 <sup>4</sup> 177.15 88.57 6 252.44 217.01 24 27.3 <sup>4</sup>			Ingiliz 1 Morse	57.39 39.83 191 44	6 197.6 92.42 12 193 53				+	
Morse Vuille-Lessard	262 142 12 211 122 47 32.3 256.86 301.15 45 145.26 106.29 255 32.0	% 51.00 [-36.59, 138.59] % 111.60 [22.65, 200.55]	+			45 185.61 38.67			+	-	
Total (95% CI)		% 47.70 [-45.73, 141.13]	-	Total (95% CI)		65		% -2.03 [-21.89, 17.83]	•		
	5045.55; Chi <sup>2</sup> = 7.55, df = 3 (P = 0.06); l <sup>2</sup> = 60%	-500	-250 0 250 500 avours No Fibrosis Favours Fibrosis	Heterogeneity: Tau <sup>2</sup> = 15 Test for overall effect: Z =		df = 3 (P = 0.19); I <sup>2</sup>	= 37%		-200 -100 Favours No Fibrosis	0 100 Faugure Eibrosic	200
(g) ALT	Fibrosis No Fibrosis	Mean Difference	Mean Difference	(h) AST Study or Subgroup	Fibrosis Mean SD Tot	No Fibrosis al Mean SD		Mean Difference IV, Random, 95% Cl	Mean Di IV, Rando	fference vm, 95% Cl	
Study or Subgroup Ingiliz	Mean         SD         Total         Mean         SD         Total         Weigh           135.67         74.02         6         89.38         49.21         24         12.5%		IV, Random, 95% Cl	Ingiliz Morse		6 71.83 56.22 2 57 60	24 5.3% 47 9.0%	8.17 [-29.33, 45.67]	_		
Morse Vuille-Lessard	90 35 12 111 177 47 15.8% 47.2 41.4 45 30.1 15.8 255 71.8%			Vuille-Lessard			255 85.7%			-	
				Total (95% CI)	6	3	326 100.0%	13.00 [4.34, 21.65]		٠	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	63 326 100.0% 166.22; Chi <sup>2</sup> = 2.71, df = 2 (P = 0.26); l <sup>2</sup> = 26%	· · ·		Heterogeneity: Tau <sup>2</sup> = 0.					-100 -50 (	50	100
Test for overall effect:			100 -50 0 50 100 vours No Fibrosis Favours Fibrosis	Test for overall effect: Z	= 2.94 (P = 0.003	1)			Favours No Fibrosis		100
	( ) IT) (			(j) Black Ethr	nicity						
(i) Duration	1 OT HIV Fibrosis No Fibrosis	Mean Difference	Mean Difference	07	Fibrosis	No Fibrosis		Odds Ratio	Odds R		
Study or Subgroup	Mean SD Total Mean SD Total Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	Study or Subgroup Crum-Cianflone	Events Total 0 2	Events Total 13 53	Weight M-ł 8.0%	H. Random, 95% Cl 0.60 [0.03, 13.29]	M-H, Randor	n, 95% Cl	
Ingiliz Morse	11.5 3.62 6 12.8 4.9 24 31.7% 14.8 7.2 12 15.7 6.8 47 20.4%			Morse Vuille-Lessard	0 12 5 45	4 47	8.6% 83.3%	0.39 [0.02, 7.68] 0.15 [0.06, 0.40]			
Vuille-Lessard	15.2 8.6 45 13.3 7.7 255 47.9%		+	Total (95% CI)	59		100.0%	0.18 [0.08, 0.44]			
Total (95% CI)	63 326 100.0%	0.31 [-1.85, 2.48]	+	Total events	5	132					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	= 0.67; Chi <sup>2</sup> = 2.43, df = 2 (P = 0.30); l <sup>2</sup> = 18% : 7 = 0.28 (P = 0.78)	-10 _	-5 0 5 10	Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z		df = 2 (P = 0.62); 02)	l <sup>2</sup> = 0%	0.1	)1 0.1 1 Favours No Fibrosis F	10 avours Fibrosis	100
, sector evenue energy		Fav	ours No Fibrosis Favours Fibrosis						reare nor loroade 1		
// \ . ! <sup></sup>											
(k) Hispan	,	Odds Ratio	Odds Ratio								
	Events Total Events Total Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl								
Crum-Cianflone Morse Vuille-Lessard	0 2 6 113 4.6% 4 12 15 47 24.7% 10 45 31 255 70.7%	3.31 [0.14, 76.26] 1.07 [0.28, 4.11] 2.06 [0.93, 4.58]									
Total (95% CI)	59 415 100.0%	1.79 [0.92, 3.50]	•								
Total events Heterogeneity: Tau <sup>2</sup>	14 52 = 0.00; Chi <sup>2</sup> = 0.84, df = 2 (P = 0.66); l <sup>2</sup> = 0%	<b></b>									
		0.01	0.1 1 10 100								
Test for overall effect	st: Z = 1.71 (P = 0.09)	Fav	ours No NAFLD Favours NAFLD								

**Fig. 4.** Forest plots for fibrosis risk factors. (a) Age, (b) male sex, (c) BMI, (d) fasting glucose, (e) triglycerides, (f) total cholesterol, (g) ALT, (h) AST, (i) duration of HIV infection, (j) black ethnicity, (k) Hispanic ethnicity. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

studies in the review examined drug class exposure and found no association with NAFLD [15,18,22,23].

Establishing the exact prevalence of NAFLD is difficult due to heterogenous data [4]. This is partly explained by inconsistent diagnostic methods; studies included in our review used USS, CT, H-MRS and CAP, all with differing sensitivities for detecting steatosis, making comparisons difficult [26]. Studies also vary in population selection. For instance, participants in two studies in this

review were drawn from specialist metabolic clinics where there were inevitably higher rates of diabetes. By contrast, other studies were drawn from less-selected general infectious disease clinics, for example [18].

Assessing the severity of NAFLD is crucial. The presence of fibrosis is the strongest predictor of liver-related morbidity in non-HIV patients with NAFLD [27], and patients with NASH are more at risk of liver fibrosis progression. The diagnosis of NASH still relies on liver histology, an invasive procedure which is more infrequently performed with the development of noninvasive markers of liver disease. Therefore, histological data are scarce, and our review included only six studies using liver biopsies. The prevalence of NASH in patients selected for liver biopsy was 42%, and significant fibrosis 22%. Clearly, this is an enriched population through the selection bias of an invasive test, and unsurprisingly noninvasive tests such as FIB-4 estimate a much lower prevalence of 4 and 6% in nonbiopsied populations, although the same two studies estimated 27 and 15% had significant fibrosis by transient elastography.

It is debated how this compares with the general population; Vodkin *et al.* [8] showed a higher rate of NASH in HIV patients (64 vs. 36%), whereas a recent systematic review reported similar results in biopsied cohorts (59%) [4]. The significant statistical heterogeneity between studies reflects the small and varied study populations, which makes an accurate study of the prevalence of severe disease difficult. This is exacerbated in the assessment of NASH by the evolution of histological definitions of the disease over the last 10 years, and one included study used a definition of NASH now not widely used, which may partly explain the unusually low prevalence (7%) in that study [15].

We found that increased BMI and fasting glucose were significantly associated with fibrosis, implying that metabolic disorders and in particular obesity-related adipose tissue dysfunction might play a key role in the development of liver fibrosis.

Taken together, these results warrant three comments. First, imaging studies suggest that NAFLD is common in HIV-monoinfected patients but limited histological data without long-term follow-up on the incidence of NASH/fibrosis in the post-HAART era mean we still do not know what the rate is of fibrosis progression as compared with HIV-negative patients with NAFLD. It is possible that although metabolic factors predominate in disease pathogenesis, HIV infection and/or drug exposure could potentiate the effects in the liver such that disease progresses with milder features of the metabolic syndrome, which may explain why some studies show NAFLD occurring in HIV-infected patients with lower BMI [28]. However, to address this question longitudinal studies with good-quality histological data are needed.

Second, patients with HIV infection and features of the metabolic syndrome require a full diagnostic workup for NAFLD. The prevalence of NAFLD is rising rapidly in the Western world in parallel with increasing obesity and the metabolic syndrome and has become a prominent cause of liver-related morbidity and requirement for liver transplantation [29]. Both NAFLD and HIV also confer increased risk of cardiovascular disease [30]. Therefore, the management of dyslipidaemia, hypertension, diabetes mellitus and obesity in a multi-disciplinary setting is therefore an essential aspect of HIV care and is already an integral service offered to patients in many centres. This needs to be combined with effective liver assessment and risk stratification with noninvasive tools such as transient elastography and/or biochemical markers (e.g. Enhanced Liver Fibrosis were and NAFLD fibrosis score) [31], to identify patients who need more dedicated input from a specialist hepatologist. However, the performance of these tools has been poorly validated in HIV monoinfected patients, and the disparity between estimates of fibrosis in the studies reporting both FIB-4 and transient elastography data highlights this point.

Third, we are entering a new era in the management of NAFLD. The mainstay of treating the disease has long been based on life style modification including weight loss and physical activity [32]. However, only a small proportion of patients successfully achieve this. Significantly, multiple new treatments are emerging for advanced disease [33]. Yet HIV infection is invariably an exclusion factor for patients enrolled in these trials. The data from this review show how therapeutic options are at least as important in patients with HIV, and it is essential such trials do not exclude HIV patients.

Our study has three main limitations: first, the small number of studies enrolled limits the interpretation of our findings. Only 10 articles were included in the review, mainly of moderate-to-low quality, and most of these studies enrolled a limited number of patients. There was variable reporting of relevant data, which reduced the number of analyses we could perform, and there were no data on disease incidence and the factors associated with this. Second, we were unable to meta-analyse data on drug class exposure, and there is no data on the impact of more modern treatment options such as integrase inhibitors. Third, our analysis on risk factors of fibrosis was heavily weighted towards a large Canadian study based on noninvasive markers [18]. Clearly, our systematic review highlights the lack of homogeneity in the assessment of NAFLD in HIV, and the urgent need for additional highquality data from a larger number of HIV-monoinfected patients with NAFLD.

#### Conclusion

NAFLD is common in HIV-monoinfected patients. Metabolic disorders are key risk factors of NAFLD independent of HIV parameters and predict its complications. The strong association between obesity and liver fibrosis in HIV-monoinfected patients supports the adipocentric concept of liver fibrogenesis in this population. This needs to be confirmed by additional studies. Our systematic review underlines the need for additional data on NAFLD in HIV infection as well as a better standardized assessment and management of the disease.

# Acknowledgements

Authors contributions: J.B.M.: study inception and design, data collection and analysis, drafting of article. A.P.: study design, data collection and analysis, critical review of article. A.J.S.: statistical analysis, created Fig. 2, critical review of article. K.P.: data collection, critical review of article. M.T.: study inception and design, data analysis, critical review of article. M.L.: study inception and design, data analysis, drafting of article. All authors approved final article. We would like to thank the following authors linked to articles included in the review who spent much time and effort providing additional data and clarifications from the original published data sets, which greatly improved the analyses that could be performed: Brian Agan, Nancy Crum-Cianflone, Seung Hyun, Patrick Ingiliz, Nelson Lee, Grace Lui, Caryn Morse, Takeshi Nishijima, Giada Sebastiani. We would like to thank Jacqueline Cousins, librarian at Imperial College London, for her invaluable help in building the literature search strategy. There was no external funding for this work.

#### **Conflicts of interest**

M.L. has served as a consultant on HIV NAFLD for MSD and GSK Healthcare and received fees from them. J.M., A.P., A.S., K.P., M.N. and M.T. have nothing to declare.

### References

- Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al., D:A:D Study Group. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet* 2014; 384:241–248.
- Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al., International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640–1645.

- Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepa*tology 2010; 52:1836–1846.
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver diseasemeta-analytic assessment of prevalence, incidence and outcomes. *Hepatology* 2015; 0:1–12.
- Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; 141:1249–1253.
- Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; 34:274–285.
- Lemoine M, Serfaty L, Capeau J. From nonalcoholic fatty liver to nonalcoholic steatohepatitis and cirrhosis in HIV-infected patients. *Curr Opin Infect Dis* 2012; 25:10–16.
- Vodkin I, Valasek MA, Bettencourt R, Cachay E, Loomba R. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther 2015; 41:368–378.
- Price JC, Seaberg EC, Latanich R, Budoff MJ, Kingsley LA, Palella FJ Jr, et al. Risk factors for fatty liver in the Multicenter AIDS Cohort Study. Am J Gastroenterol 2014; 109: 695–704.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Reprinted from Annals of Internal Medicine). *Phys Ther* 2009; 89:873–880.
- Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies – NHLBI, NIH. Available at: https://www. nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascularrisk-reduction/tools/cohort.
- 12. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. West Sussex, UK: John Wiley; 2009.
- 13. Higgins JPT. Cochrane handbook for systematic reviews of interventions. West Sussex: John Wiley; 2006, 265.
- 14. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010; 36:1–48.
- Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, et al. Nonalcoholic fatty liver disease among HIVinfected persons. J Acquir Immune Defic Syndr 2009; 50: 464–473.
- Sterling RK, Smith PG, Brunt EM. Hepatic steatosis in human immunodeficiency virus: a prospective study in patients without viral hepatitis, diabetes, or alcohol abuse. J Clin Gastroenterol 2013; 47:182–187.
- Morse CG, McLaughlin M, Matthews L, Proschan M, Thomas F, Gharib AM, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. *Clin Infect Dis* 2015; 60:1569–1578.
- Vuille-Lessard E, Lebouché B, Lennox L, Routy JP, Costiniuk CT, Pexos C, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV mono-infected patients. *AIDS* 2016; 30: 2635–2643.
- Ingiliz P, Valantin MA, Duvivier C, Medja F, Dominguez S, Charlotte F, et al. Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 monoinfected patients on antiretroviral therapy. *Hepatology* 2009; 49:436–442.
- Lemoine M, Barbu V, Girard PM, Kim M, Bastard JP, Wendum D, et al. Altered hepatic expression of SREBP-1 and PPAR gamma is associated with liver injury in insulinresistant lipodystrophic HIV-infected patients. *AIDS* 2006; 20:387–395.
- Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, et al. Nonalcoholic fatty liver disease in HIVinfected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. *Clin Infect Dis* 2008; 47: 250–257.
- 22. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Nozaki Y, Nagata N, et al. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. *PLoS One* 2014; 9: e87596.

- Lui G, Wong VWS, Wong GLH, Chu WC, Wong CK, Yung IM, et al. Liver fibrosis and fatty liver in Asian HIV-infected patients. Aliment Pharmacol Ther 2016; 44:411–421.
- Li Vecchi V, Soresi M, Giannitrapani L, Di Carlo P, Mazzola G, Colletti P, et al. Prospective evaluation of hepatic steatosis in HIV-infected patients with or without hepatitis C virus co-infection. Int J Infect Dis 2012; 16:e397–e402.
- 25. Anstee QM, McPherson S, Day CP. How big a problem is nonalcoholic fatty liver disease? *BMJ* 2011; 343:201.
- 26. Castera L. Noninvasive evaluation of nonalcoholic fatty liver disease. Semin Liver Dis 2015; **35**:291–303.
- Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; 61:1547–1554.
   Mohammed SS, Aghdassi E, Salit IE, Avand G, Sherman M,
- Mohammed SS, Aghdassi E, Salit IE, Avand G, Sherman M, Guindi M, et al. HIV-positive patients with nonalcoholic fatty liver disease have a lower body mass index and are more physically active than HIV-negative patients. J Acquir Immune Defic Syndr 2007; 45:432–438.

- Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; 148:547–555.
- Crum-Cianflone N, Krause D, Wessman D, Medina S, Stepenosky J, Brandt C, Boswell G. Fatty liver disease is associated with underlying cardiovascular disease in HIV-infected persons. *HIV Med* 2011; 12:463–471.
- European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63:237–264.
- Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015; 149:367–378.e5.
- Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. Nat Rev Gastroenterol Hepatol 2016; 13:196–205.